

**Diastereoselective Synthesis of *syn*-1,3-Polyols and
Studies towards the C1-C31 and C32-C52 Fragments of
Amphidinol 3**

Thesis submitted in accordance with the requirements of the
University of Liverpool for the Doctor in Philosophy

By

Aleksandr Grišin

September 2012

Abstract

Diastereoselective Synthesis of *syn*-1,3-Polyols

The stereoselective construction of polyacetate 1,3-diols has attracted considerable attention due to the ubiquity of this motif in complex biologically active polyene macrolides (amphotericin B, RK-397, mycoticin, candidin). We have developed a highly stereoselective bismuth(III)-mediated two-component hemiacetal/*oxa*-conjugate addition reaction, which directly provides *syn*-1,3-diols in the form of cyclic acetals having an adjacent electron-withdrawing group in the form of aldehydes and ketones. The scope and limitations of this transformation were examined and culminated with the synthesis of the C18-C28 fragment of antibiotic RK-397.

Studies towards the C1-C31 and C32-C52 Fragments of Amphidinol 3

Temporary-tethered reactions provide an important strategy for target-directed synthesis, since they circumvent the problems encountered with entropically unfavorable reactions. The temporary silicon-tethered ring-closing metathesis (TST-RCM) allows for the highly (*Z*)-selective coupling of mixed silaketals in the formation of the medium sized rings. The latter compounds can undergo a substrate controlled stereoselective electrophilic functionalisation, for example, hydroboration, dihydroxylation or epoxidation, and produce polyoxygenated motifs that are present in many biologically important natural products.

In the course of these studies we have developed a highly convergent asymmetric synthesis of the C1-C31 polyol fragment of amphidinol 3, where the TST-RCM/hydroboration reaction is successfully employed for the efficient coupling

of the C16-C23 and C24-C30 units of the natural product with concomitant introduction of the crucial propionate-type C23-C24 stereocentres.

In the final part of thesis the investigation of the stereoselective dihydroxylation reaction of mixed *syn* and *anti* eight-membered cyclic silaketals was carried out. The resulting oxygenated products can be efficiently transformed *via* an *intramolecular* cyclisation of δ -hydroxy epoxides into the highly substituted *syn*- and *anti*-tetrahydropyrans (THPs), a strategy that could also have application in related natural products, for example, ladder polyether polyketides. The merit of the developed methodology was highlighted in the asymmetric synthesis of the common C31(52)-C39(44) THP fragment of amphidinol 3, which could be ultimately used in the bidirectional route towards the *bis*-THP segment of the natural product.

Acknowledgements

I would like to acknowledge my research supervisor Professor P. Andrew Evans for the opportunity to conduct research and continued support through the years. His unfettered patience, guidance and high-standards have allowed me to develop as a scientist and laid the foundation for the following steps in my career.

I also thank Katie Evans for taking care of the day-to-day organisation and administration of the Evans' group.

I would extend my appreciation to all Evans' group members past and present for making an outstanding atmosphere during the studies and for constructive advices and discussions during group meetings. I am particularly grateful to an outstanding scientist Dr. Sergio Maroto for his endless aid and extremely valuable suggestions, which helped me to grow as a chemist.

The entire process of writing this thesis would have been much more difficult if not for the proofreading of my co-workers. I would like to specially acknowledge Dr. Phillip A. Inglesby, Tomass Baikstis, Ryan O'Connor, Stephanie Yip and Dr. Samuel Oliver. Thank you guys!

I would like to appreciate the University of Liverpool for financial support.

I would like to thank my parents, Aleksandr and Svetlana, for their everlasting love, support and faith in me over all these years. Without their help and encouragement this degree would not have been possible. I would like to especially acknowledge my aunt Tanya for her invaluable support back in the days and helpful suggestions.

Finally, I would like to thank my partner, Julija Aleksina, for her love, support and commitment over the last four years. Love you.

For my family

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List of Publications

1. Evans, P. A.; Grisin, A.; Lawler, M. J. "Diastereoselective construction of *syn*-1,3-dioxanes via a bismuth-mediated two-component hemiacetal/oxa-conjugate addition reaction." *J. Am. Chem. Soc.* **2012**, *134*, 2856.

List of Abbreviations

Å	angstrom
Ac	acetyl
Acac	acetylacetonate
Alloc	allyloxycarbonyl
AIBN	azobisisobutyronitrile
^t Am	<i>tert</i> -Amyl
aq.	aqueous
Ar	aryl
APT	attached proton test
Bn	benzyl
Bz	benzoyl
ⁿ Bu	butyl
^t Bu	<i>tert</i> -butyl
9-BBN	9-borabicyclo[3.3.1]nonane
BINOL	1,1'-bi-2-naphthol
BINAP	2,2'- <i>bis</i> (diphenylphosphino)-1,1'-binaphthyl.
bmim	1-butyl-3-methylimidazolium
BOC	<i>tert</i> -butoxycarbonyl
BOC-ON	2-(<i>tert</i> -butoxycarbonyloxyimino)-2-phenylacetonitrile
BOM	benzyloxymethyl
b.r.s.m.	based on recovered starting material
°C	degrees Celsius
CAN	ceric ammonium nitrate
<i>cat.</i>	catalytic
CBS	Corey-Bakshi-Shibata
<i>cee</i>	conservation of enantiomeric excess
CI	chemical ionization
COSY	¹ H- ¹ H correlation spectroscopy
CSA	(±)-10-camphorsulphonic acid
Cp	cyclopentadienyl
Cy	cyclohexyl

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DHQD-IND	(9- <i>O</i> -indolinylcarbamoyl) dihydroquinidine
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DIPT	diisopropyl tartrate
DMP	Dess–Martin periodinane
2,2-DMP	2,2-dimethoxypropane
DMS	dimethylsulfide
DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DTBMP	di- <i>tert</i> -butyl-4-methylpyridine
dppf	1,1'- <i>bis</i> (diphenylphosphino)ferrocene
<i>ds</i>	diastereoselectivity
EC ₅₀	half maximal effective concentration
EtOAc	ethyl acetate
<i>ee</i>	enantiomeric excess
ESI	electrospray ionization
<i>ent</i>	enantiomer
Et	ethyl
equiv	equivalent
EWG	electron-withdrawing group
Fm	9-fluorenylmethoxy
FTIR	fourier transform infra-red
g	gram
G-II	Grubbs 2 nd generation catalyst

HG-II	Hoveyda-Grubbs 2 nd generation catalyst
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HPMA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HSQC	heteronuclear single quantum coherence
HMBC	heteronuclear multiple-bond correlation spectroscopy
HRMS	high resolution mass spectrometry
HWE	Horner–Wadsworth–Emmons
IBX	2-iodoxybenzoic acid
IC ₅₀	half maximal inhibitory concentration
Ipc	isopinocampheyl
ISMS	intramolecular silyl-modified Sakurai reaction
IMSC	intramolecular Sakurai cyclisation
<i>J</i>	coupling constant (NMR)
KO ^t Bu	potassium <i>tert</i> -butoxide
LDA	lithium diisopropylamide
LiDBB	4,4'-di(<i>tert</i> -butyl)biphenylide
L-Selectride	lithium tri- <i>sec</i> -butylborohydride
Me	methyl
MEC	minimal effective concentration
MPA	α -methoxy- α -(trifluoromethyl)phenylacetyl
MHz	megahertz
mL	milliliter
mmol	millimole
MOM	methoxymethyl
MIB	morpholino isoborneol
mp	melting point
MS	molecular sieves
Ms	methylsulfonyl
MSA	<i>N</i> -methyl- <i>N</i> -trimethylsilylacetamide

MTBSTFA	<i>N</i> - <i>tert</i> -butyldimethylsilyl- <i>N</i> -methyltrifluoroacetamide
nm	nanometre
NCS	<i>N</i> -chlorosuccinimide
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMO	4-methylmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
NMO	4-methylmorpholine- <i>N</i> -oxide
Naph	naphthyl
Nu	nucleophile
n/a	no activity
n/r	no reaction
n/d	not determined
Ph	phenyl
Piv	pivoyl
PPA	polyphosphoric acid
PPTS	pyridinium <i>p</i> -toluenesulfonic acid
ppm	parts per million
PMB	<i>p</i> -methoxybenzyl
PMP	<i>p</i> -methoxyphenyl
PNB	<i>p</i> -nitrobenzyl
PT	1-phenyl-1 <i>H</i> -tetrazole-5-yl
PTSA	<i>p</i> -toluenesulfonic acid
PTSH	1-phenyl-1 <i>H</i> -tetrazole-5-thiol
Py	pyridine
Pyrr	pyrrolidine
rac	racemic
ⁱ Pr	isopropyl
RCM	ring-closing metathesis
R _f	retention factor

RT	room temperature
SBox	<i>S</i> -benzoxazolyl
SEM	2-(trimethylsilyl)ethoxymethyl
STaz	<i>S</i> -thiazoliny
TAS-F	<i>tris</i> (dimethylamino)sulfonium difluorotrimethylsilicate
TBACl	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDMSIM	1-(<i>tert</i> -butyldimethylsilyl)imidazole
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
t_R	retention time
Tr	triphenylmethyl
Ts	<i>p</i> -toluenesulfonyl
TST	temporary silicon-tethered
μL	microliter

Was mich nicht umbringt, macht mich stärker.

Friedrich Wilhelm Nietzsche

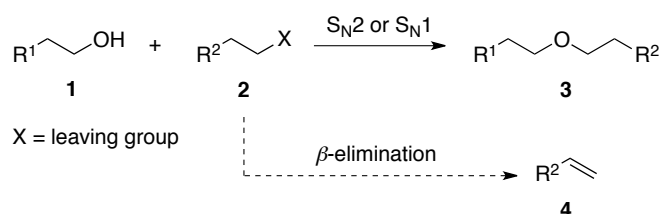
Chapter 1

Bismuth(III)-catalysed C-O bond forming transformations

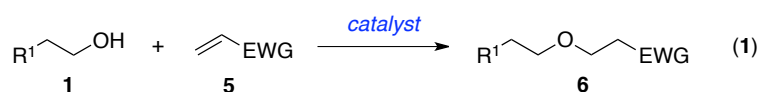
1.1 Introduction

The formation of the carbon–oxygen bond is one of the most widely used functional group transformations in organic synthesis.¹ The classical Williamson etherification is limited, in a practical sense, to the alkylation of an alkoxy anion with an alkyl halide or sulfonate under basic conditions.² Unfortunately, the formation of olefins can often occur *via* an elimination pathway when secondary electrophiles are employed and become a major side-reaction in the case of tertiary substrates, thus dramatically limiting the scope of the transformation (Scheme 1.1.1).

Scheme 1.1.1: *Ether Synthesis Using Aliphatic Substitution Reaction*

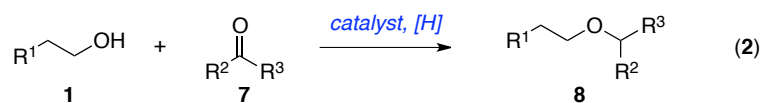


In order to overcome the abovementioned limitations, new milder routes are being developed for this type of transformation. The *oxa*-Michael addition is the direct and simple method for the synthesis of symmetrical and unsymmetrical ethers. Typically, two modes of the activation are applicable to this reaction, consisting of base activation of the nucleophile and/or Lewis/Brønsted acid-mediated electrophilicity enhancement of the conjugate acceptor (eq. 1).³



Another attractive alternative for the efficient C-O bond formation is the reductive etherification (eq. 2). Similar to *oxa*-Michael addition, this reaction relies

on a Lewis acid activation of the carbonyl group followed by *intermolecular* hydride transfer.



During the last two decades, bismuth(III) derivatives have emerged as relatively non-toxic and non-carcinogenic, easy to handle and moisture insensitive reagents, with the ability to act as both Lewis and Brønsted acids and successfully catalyse a plethora of useful transformations.⁴ This has resulted in their application as ‘green reagents’ in the development of methods for the formation of symmetrical and unsymmetrical ethers under essentially non-basic conditions.

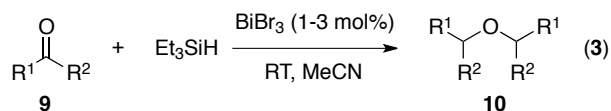
The following chapter will outline recent progress in the area of bismuth(III)-catalysed etherification with a special emphasis of the reaction scope and its application in the target-oriented synthesis.

1.2 Intermolecular Etherification

In 1997, Komatsu *et al.* were the first to show that carbonyl compounds undergo a reductive *homo-* or *heterocoupling* with alkoxysilanes in the presence of catalytic amount of bismuth(III) bromide to afford the corresponding symmetrical and unsymmetrical ethers, respectively, and applied this reaction for the preparation of novel macrocyclic ethers.⁵ The advantage of the methodology relied on the mild non-basic reaction conditions, which avoided elimination. Generally, the reactions were fast and furnished the *homoetherification* products in less than 5 minutes when aromatic aldehydes were used as substrates (eq. 3, Table 1.2.1, entry 1). The reaction of aliphatic aldehydes (entry 2) and aliphatic ketones (entry 4 and 5)

required longer reaction times, however the *homo*etherification of phenyl methyl ketone failed, with a trace of product being observed after 20 hours (entry 6).

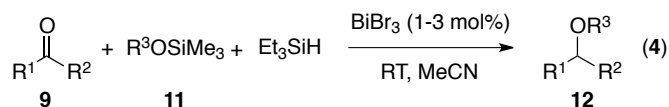
Table 1.2.1: *Synthesis of Symmetrical Ethers via the BiBr₃-Catalysed Homocoupling Reaction (eq. 3)*



Entry	R ¹	R ²	Time	Yield (%)
1	Ph	H	<5 min	84
2	Me(CH ₂) ₆	H	2 h	88
4	-(CH ₂) ₅ -		2 h	72
5	PhCH ₂ CH ₂	Et	2 h	61
6	Ph	Me	20 h	trace

The superiority of the reductive coupling over the conventional etherification becomes more obvious in the case of formation of the unsymmetrical ethers (eq. 4, Table 1.2.2). Benzyl and 2-octyl trimethylsilyl ethers reacted readily with aliphatic and aromatic aldehydes (entries 1-3, 9) and ketones (entries 4, 6 and 10). However, acetophenone and methyl vinyl ketone showed sluggish reactivity (entries 5 and 7). Interestingly, a similar reactivity trend is observed in the *homocoupling* reaction. Thus, these results indicate a unique ability of BiBr₃ to discriminate phenyl ketones from alicyclic and cyclic derivatives, in contrast to other reported Lewis acids such as TMSOTf and trityl perchlorate,⁶ which failed to deliver the requisite chemoselectivity.

Table 1.2.2: *Synthesis of Unsymmetrical Ethers via the BiBr₃-Catalysed Heterocoupling Reaction (eq. 4)*

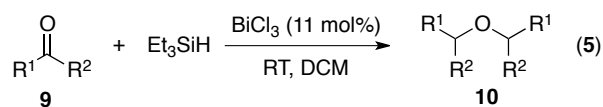


Entry	R ¹	R ²	R ³	Time	Yield (%)
1	Ph	H	PhCH ₂ -	<5 min	84
2	Me(CH ₂) ₆	“	“	“	88
3	<i>trans</i> -MeCH=CH	“	“	2 h	61
4	-(CH ₂) ₅ -	“	“	<5 min	89
5	Ph	Me	“	20 h	trace
6	Me(CH ₂) ₅	“	“	1 h	96
7	CH ₂ =CH	“	“	20 h	trace
8	Ph	H	Ph	1 h	0 ^a
9	Ph	“	2-octyl	“	81
10	PhCH ₂	Et	“	“	88

^aDibenzyl ether was the only product obtained.

Wada and co-workers showed that BiCl₃ is able to catalyse *homo*- and *heterocoupling* of carbonyl compounds with non-protected alcohols.⁷ This method is synthetically convenient, as the preparation of silyl ethers is avoided, and makes the overall procedure more atom-economical. Various symmetrical ethers were obtained under mild reaction conditions as shown in eq. 5, Table 1.2.3. Benzaldehyde (entry 1) and aliphatic aldehydes (entries 2, 3) reacted smoothly to afford the corresponding symmetrical ethers in good yields. Notably, ketones generally gave lower yields (entries 5, 6), while the sluggish reactivity of phenyl methyl ketone was attributed to steric factors (entry 7). Remarkably, the reaction of 3-hydroxybenzaldehyde proceeded chemoselectively without the need to mask the phenolic hydroxyl group (entry 4).

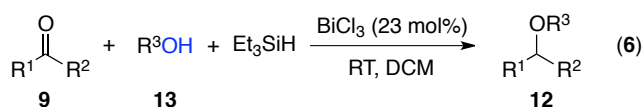
Table 1.2.3: *Ether Synthesis Using Carbonyl Compounds and Et₃SiH in the Presence of BiCl₃ (eq. 5)*



Entry	R ¹	R ²	Yield (%)
1	Ph	H	87
2	PhCH ₂ CH ₂	“	90
3	Cy	“	85
4	<i>m</i> -HOC ₆ H ₄	“	90
5	PhCH ₂ CH ₂	CH ₃	50
6	CH ₃ CH ₂ CH ₂ CH ₂	“	29
7	Ph	“	trace

Table 1.2.4 summarises the carbonyl derivatives scope in the reductive etherification with primary and secondary alcohols (eq. 6). Generally, aldehydes gave higher yields than ketones (entries 1-8, 12 vs. 9-11), while the reactivity of primary and secondary alcohols in terms of yield was similar. Notably, phenols as well as *tert*-butyl alcohol were shown to be inert under the reaction conditions. The chemoselectivity of the transformation was remarkable, owing to the fact that phenol and carboxyl group containing substrates could be used without protection of their functional groups, which contributed to the overall synthetic efficiency.

Table 1.2.4: *Ether Synthesis Using Carbonyl Compounds and Alcohols Mediated by BiCl₃ and Et₃SiH (eq. 6)*



Entry	R ¹	R ²	R ³	Yield (%)
1	Ph	H	CH ₃ CH ₂	74
2	“	“	PhCH ₂	80
3	“	“	PhCH ₂ CH ₂ (CH ₃)CH	82
4	PhCH ₂	“	PhCH ₂ CH ₂	61
5	CH ₃ (CH ₂) ₇	“	PhCH ₂ CH ₂	63
6	“	“	PhCH ₂ CH ₂ (CH ₃)CH	64
7	Cy	“	PhCH ₂ CH ₂	77
8	“	“	PhCH ₂ CH ₂ (CH ₃)CH	70
9	PhCH ₂ CH ₂	CH ₃	CH ₃ CH ₂	24
10	Ph	“	PhCH ₂ CH	29
11	-(CH ₂) ₅ -	“	“	38
12	Ph	H	HOOC(CH ₂) ₁₁	75

Bajwa and co-workers reinvestigated the BiBr₃/Et₃SiH mediated reductive alkylation of silyl ethers.⁸ They showed that the process was actually catalysed by *in situ* formed triethylsilyl bromide, which was generated through the reduction of BiBr₃ with Et₃SiH. In addition, the scope of the reductive etherification was extended to triisopropylsilyl- and *tert*-butyldimethylsilyl ethers (eq. 7, Table 1.2.5).

Table 1.2.5: Transformation of Silyl Ethers into Dialkyl Ethers (eq. 7)
$$\begin{array}{c}
 \text{R}^1\text{OSiR}_3 + \text{R}^2\text{COR}^3 \xrightarrow{\text{Et}_3\text{SiH, cat. BiBr}_3} \text{R}^1\text{-O-}\begin{array}{c} \text{R}^2 \\ | \\ \text{R}^3 \end{array} \quad (7) \\
 \text{14} \qquad \qquad \text{15} \qquad \qquad \qquad \qquad \text{16}
 \end{array}$$

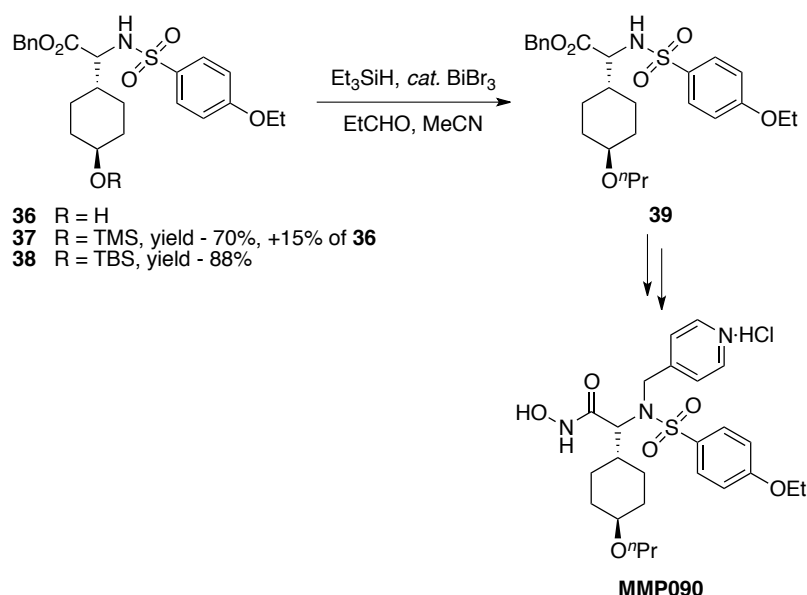
Entry	Silyl ether	Aldehyde or ketone	Product	Yield (%)
1				92
2				90
3				85
4				92
5				81
6				87
7				45
8			n/r	0

Typically, yields of the reductive etherification were high and the reaction was completed after 15-30 minutes. The transformation proceeded smoothly with both aliphatic and aromatic aldehydes as well as ketones. Bulky silyl ethers such as TIPS and TBDMS (entries 1, 3-6) worked well, while TBDPS ether showed

somewhat lower reactivity (entry 7). Remarkably, the bromide containing substrate was tolerated, demonstrating the superiority of the reductive etherification conditions (entry 5). However, sterically hindered and electronically deactivated silyl ethers were unreactive (entry 8).

The *intramolecular* bismuth(III) catalysed etherification was successfully applied in the synthesis of the dual matrix metalloprotease/tumor necrosis factor inhibitor MMP090 (Scheme 1.2.1).^{8a,c}

Scheme 1.2.1: *Application of the Reductive Etherification in the Synthesis of MMP090*

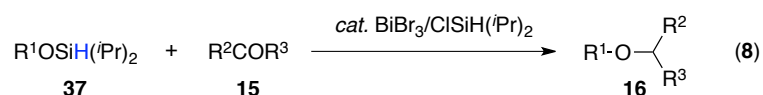


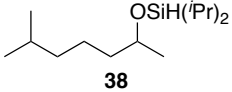
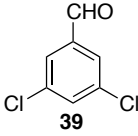
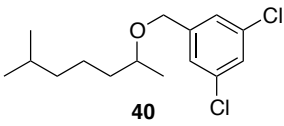
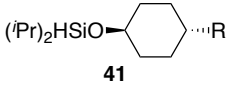
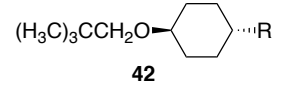
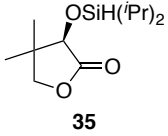
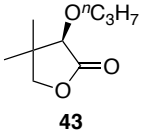
Initial alkylation of **36** using conventional methods ($\text{NaH}/\text{THF}/^n\text{PrBr}$; $\text{NaH}/\text{THF}/\text{allyl bromide}$; $\text{NaH}/\text{THF}/^n\text{PrBr}/18\text{-crown-6/}$ and $\text{NaH}/\text{DMF}/\text{allyl bromide}$) failed due to the hindered nature of the secondary alcohol as well as presence of the base-sensitive α -aminoester, which was susceptible to epimerisation. Gratifyingly, application of the reductive alkylation afforded the required **39** in 70% yield from the TMS ether **37** or 88% yield from TBS ether **38** on a remarkable 50 kg scale.

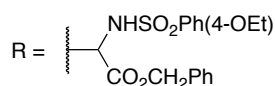
The same research group reported etherification of alkoxydialkylsilanes with carbonyl compounds using catalytic BiBr_3 and chlorodiisopropylsilane (eq. 8).⁹ The

crucial improvement of this method is the application of the alkoxysilanes, containing an internal hydride source, instead of triethylsilane, which is generally used in excess amounts. Interestingly, the addition of the catalytic chlorosilane was shown to be crucial in order to drive the reaction to completion.

Table 1.2.6: *BiBr₃/ClSiH(*i*Pr)₂ Mediated Reductive Etherification of Alkoxysilanes (eq. 8)*



Entry	Alkoxysilane	Carbonyl compound	Product	Yield (%)
1	PhCH ₂ OSiH(<i>i</i> Pr) ₂	PhCHO	(PhCH ₂ O) ₂	90
2	“	(CH ₃) ₃ CHO	PhCH ₂ OCH ₂ CH(CH ₃) ₂	89
3	“	CH ₃ COCH ₃	PhCH ₂ OCH(CH ₃) ₂	88
4	Ph(CH ₂) ₂ OSiH(<i>i</i> Pr) ₂	CH ₃ COCH ₃	Ph(CH ₂) ₂ OCH(CH ₃) ₂	91
5	“	CH ₃ CH ₂ CHO	Ph(CH ₂) ₂ O(CH ₂) ₂ CH ₃	82
6	“	(<i>E</i>)-PhCH=CHCHO	(<i>E</i>)-Ph(CH ₂) ₂ OCH ₂ (CH) ₂ Ph	89
7	Br(CH ₂) ₃ OSiH(<i>i</i> Pr) ₂	PhCHO	Br(CH ₂) ₃ OCH ₂ Ph	91
8				85
9		(CH ₃) ₃ CCHO		92
10		CH ₃ CH ₂ CHO		trace

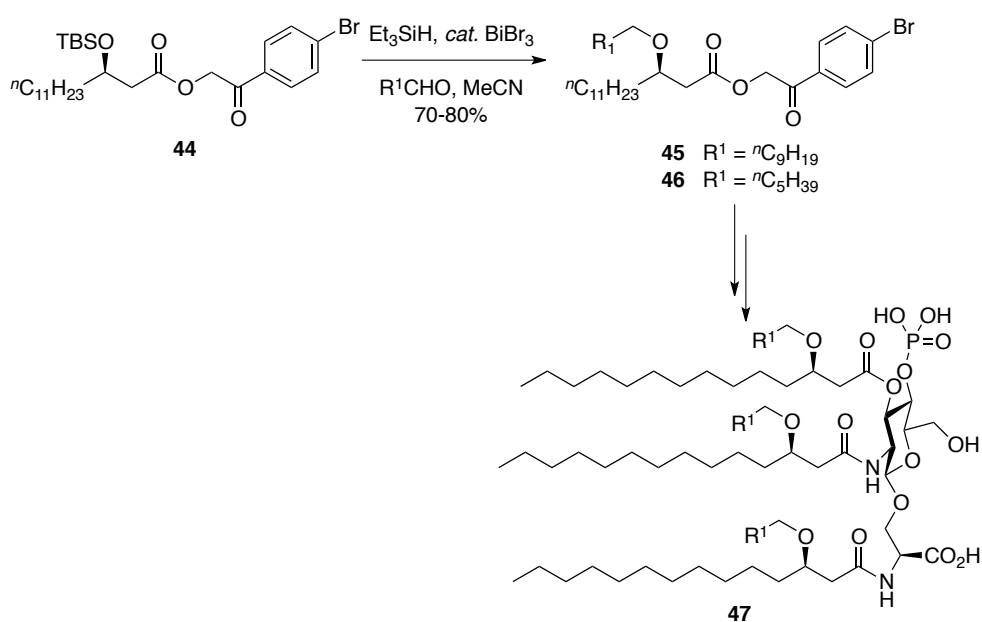


The results presented in Table 1.2.6 correlate with the previous report (*vide supra*). Primary and secondary alkoxysilanes reacted with aliphatic and aromatic

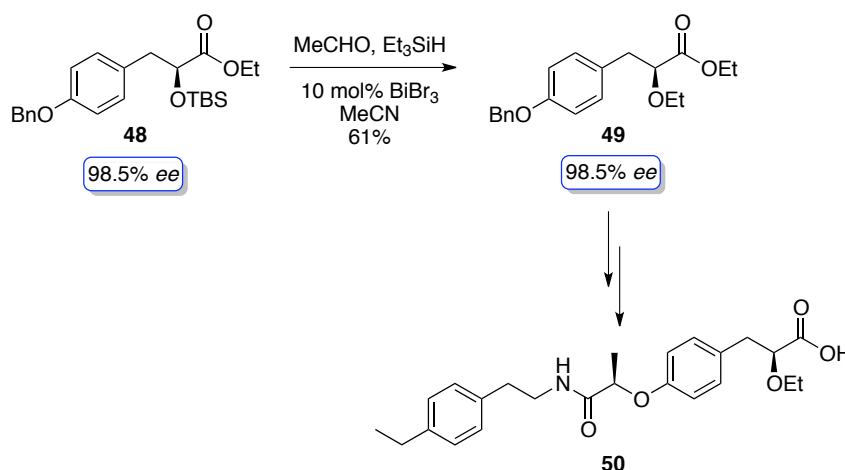
aldehydes and ketones very efficiently and afforded the alkylation products in high yields (entries 1-9), whereas sterically hindered and deactivated silyl ethers were unreactive (entry 10).

Johnson and co-workers applied the *intermolecular* reductive etherification in the preparation of AGP lipid A mimetics (Scheme 1.2.2).¹⁰ The reductive etherification of the enantioenriched **44** with decanal or hexanal in presence of BiBr₃ allowed for the smooth preparation of **45** and **46** in 70-80% yield on a gram-scale. This was in great contrast with other routes to 3-alkyloxytetradecanoic acids, which consisted of the multi-step sequences with low reported yields.¹¹

Scheme 1.2.2: *Reductive Etherification in the Preparation of AGP Lipid A Mimetics*

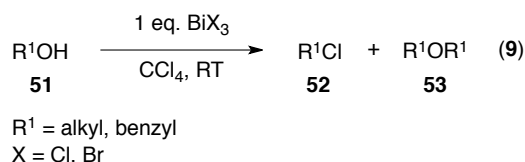


Another important example included the application of the reductive alkylation in the synthesis of a peroxime proliferator activated receptor (PPAR) α/γ agonist **50** (Scheme 1.2.3).¹² The reductive etherification of the TBS derivative **48** with acetaldehyde proceeded with 61% yield and most importantly with complete retention of the configuration on the easily epimerisable α -hydroxy ester moiety.

Scheme 1.2.3: Reductive Etherification in the Preparation of PPAR α/γ Agonist **50**

Unfortunately, the substantial amount (21%) of the starting material was recovered during the process. The application of the reaction to other silyl ethers was unsuccessful and resulted in 15% and 30% yield for TMS and TES derivatives, respectively. It is noteworthy that the formation of ethyl ether under basic conditions (NaH, NaHMDS, KHMDS, K₂CO₃ or NaO^tAmyl/EtI) gave various degrees of epimerisation (2-30%) and inseparable side products.

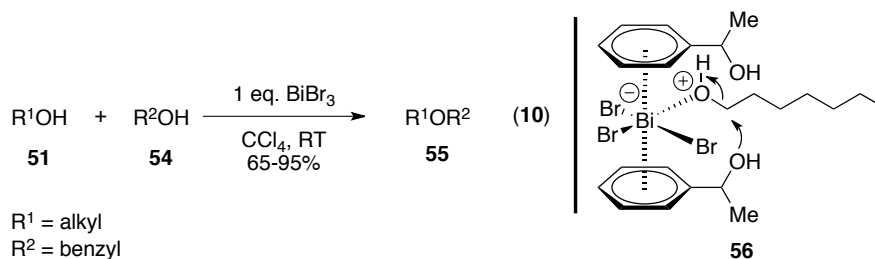
The construction of ethers directly from two alcohols is extremely synthetically attractive. However, this transformation usually requires harsh reaction conditions and strong Lewis or Brønsted acids. Boyer and co-workers, in the course of an investigation into the chlorination of alcohols using BiCl₃, discovered that a Bi(III) halide converts benzylic alcohols to symmetrical ethers with only minor amounts of the corresponding chlorides (eq. 9).¹³



Interestingly, in the presence of BiBr₃, the ethers were obtained quantitatively in 15 minutes at ambient temperature. The reaction was investigated further and a

convenient route for the protection of aliphatic alcohols with various benzylic carbinols was developed (eq. 10, Scheme 1.2.4).¹⁴

Scheme 1.2.4: *Postulated Mechanism for the Benzylation of Aliphatic Alcohols*



The results of the study showed that ether synthesis could be achieved using primary, secondary and tertiary alcohols in very high yield and the only by-products observed were symmetrical benzylic ethers. The reactivity of the branched benzylic alcohols was higher than non-branched ones and the full conversion of the latter required extended reaction times, but yields were still high. Hence, BiBr₃ showed the unique chemoselectivity in the etherification reaction based on the electronic properties of the participating alcohol. As a working model, the authors proposed a ferrocene-like sandwich structure **56**, with BiBr₃ in a *hexacoordinated* state. The Lewis acid activation of the hydroxyl group could make it a better leaving group and predispose towards the *intramolecular* benzylic oxygen attack. Although the methodology provides a wide range of sterically hindered ethers in excellent yields (Figure 1.2.1), the transformation proceeds in the environmentally non-friendly CCl₄, which precludes its application on a large scale.

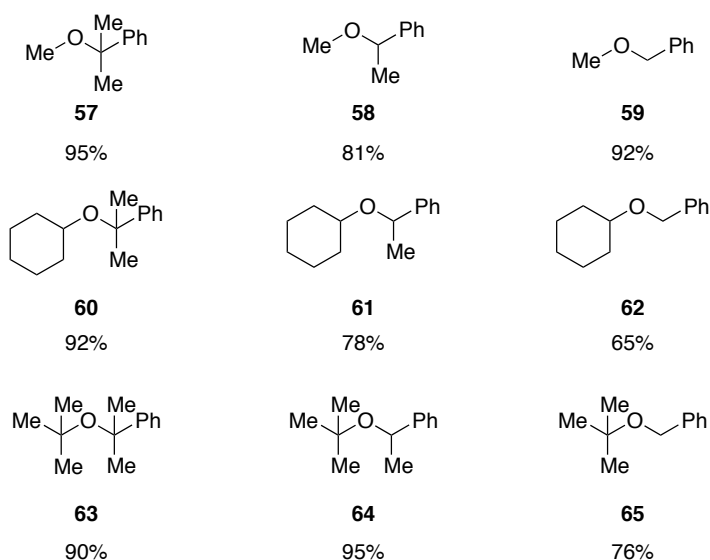
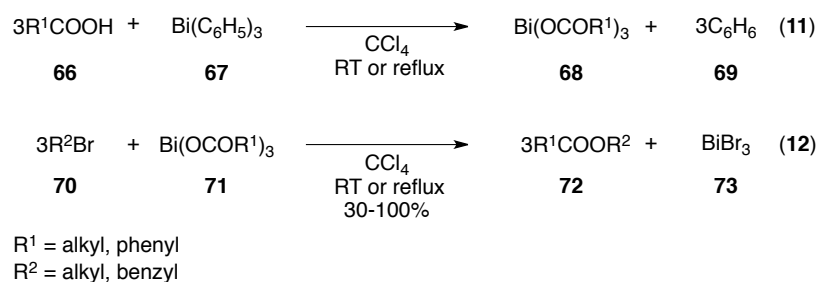


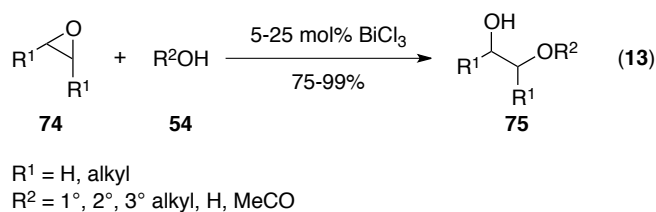
Figure 1.2.1: Selected Examples of BiBr_3 Mediated Alcohol Protection as the Benzyl-Type Ethers

In 2001, the same group reported the selective bismuth(III)-mediated protection of carboxylic acids, which was based on the Hard and Soft Acids and Bases (HSAB) principle of Pearson (eq. 11 and 12).¹⁵ The stoichiometric reaction of the carboxylic acid **66** with triphenylbismuth **67** afforded the bismuth(III) carboxylate **68**.



Subsequent addition of the aliphatic bromide promoted the ligand exchange reaction and afforded the protected carboxylic acid **72**. Notably, almost quantitative yields were achieved with *tert*-butyl and benzyl bromides. In contrast, primary bromides did not participate in the transformation, while secondary counterparts afforded various mixtures of esters and alkene elimination products. It is noteworthy that the scope of the reaction could be extended to tosylic acids.

Mohammadpoor-Baltork *et al.* demonstrated the utility of bismuth(III) chloride in the regio- and stereoselective opening of epoxides with oxygen nucleophiles (eq. 13).¹⁶

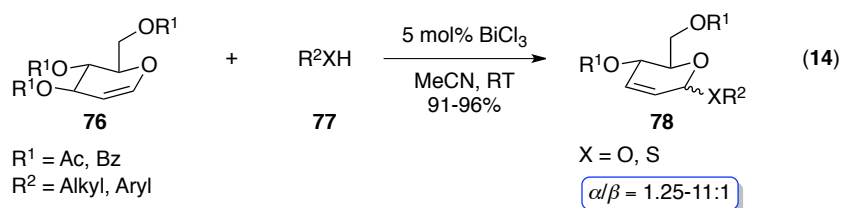


With unsymmetrical epoxides, nucleophilic attack occurred at the less-substituted oxirane carbon, while styrene oxide gave the more substituted product. Generally, more hindered nucleophiles required higher catalyst loadings and elevated temperatures, however yields remained exceptionally high. It is noteworthy that the transformation worked very efficiently with other *O*-nucleophiles such as acids and water to furnish hydroxy esters and diols respectively (yields up to 98%).

1.3 Etherification via *O*-Glycosylation

2,3-Unsaturated glycosides and pseudoglycols are important intermediates in the synthesis of glycopeptides, nucleosides, modified sugars and other biologically active natural products.¹⁷ 2-Deoxy and 2,3-dideoxy carbohydrates derived from 2,3-unsaturated-*O*-glycosides are crucial building blocks present in a variety pharmaceutical drugs that include vancomycin, erythromycin and daunomycin.¹⁸ Thus, new methods that deliver these synthons are of interest and one of the foremost reactions to access these compounds is the Lewis acid catalysed allylic rearrangement of glycols.

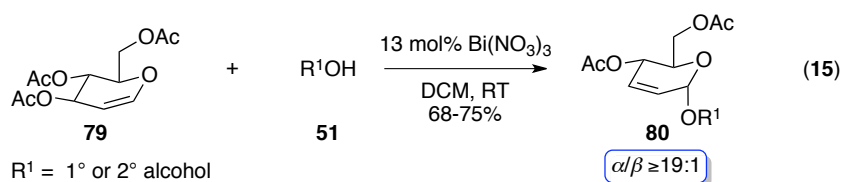
In 2002, Venkateswarlu *et al.* were the first to use bismuth(III) chloride as a Lewis acid for the synthesis of diverse *O*- and *S*-glucopyranosides *via* Ferrier rearrangement (eq. 14).¹⁹



The transformation allowed smooth preparation of structurally diverse glucopyranosides with good anomeric selectivity and almost quantitative yield with no by-products. The broad scope of nucleophiles included primary, secondary alkyl and aryl alcohols as well as *N*-Boc-protected β -hydroxy α -amino acids.

A few years later, Vankar and co-workers discovered that the same transformation could be catalysed by bismuth(III) triflate.²⁰ In contrast to BiCl_3 system, the reaction went to completion in minutes, albeit with lower yields. Increased surface area of the catalyst appeared to be beneficial to this reaction. Thus, bismuth(III) triflate supported on the silica gel was shown to improve the α -selectivity of the glycosylation in some cases as well as the yield.

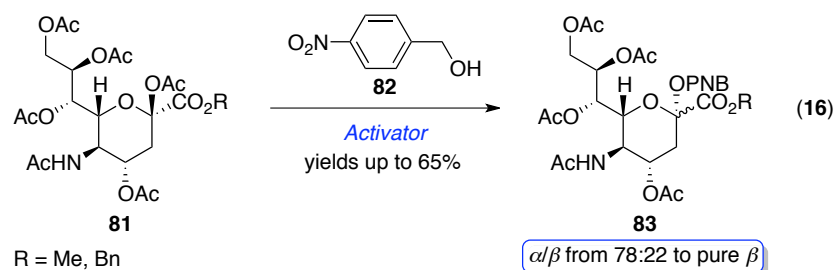
Banik *et al.* investigated the Ferrier *O*-glycosylation of 3,4,5-tri-*O*-acetyl D-glucals catalysed by bismuth(III) nitrate (eq. 15).²¹ In contrast to other reports in the field, they found that glycosylation of alcohols proceeded in a stereospecific manner and only the α -anomers of the desired product were produced.



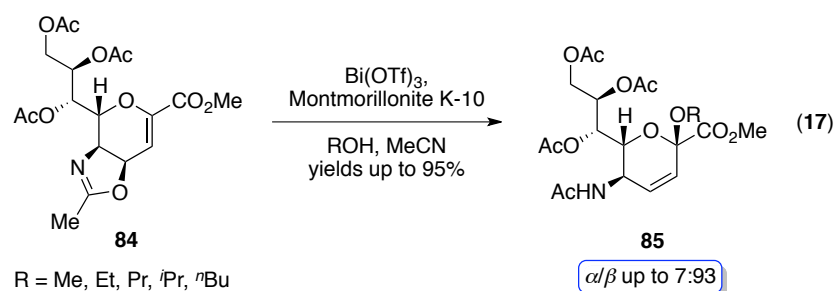
Another important input to the subject field was from the Salunkhe group, who probed various metal nitrates as possible catalysts for the Ferrier *O*-glycosylation, and found that bismuth(III) nitrate outperformed Fe, Cu, Cr, Ce, Ni and Co nitrates.²² Additionally, the solvent effect on the reaction was studied. It was showed that hydrophobic ionic liquids, such as $[\text{bmim}][\text{PF}_6]$, were superior to

conventional solvents in terms of yield and reaction time and allowed the medium to be recycled up to five times without reducing the efficacy.

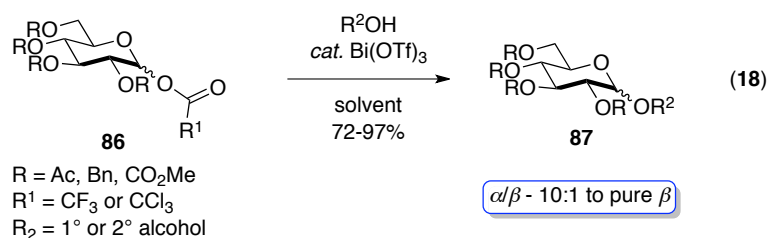
Ikedo and co-workers investigated *O*-glycosylation of sialyl acetates in the presence of various Lewis acids (eq. 16).²³ In this context, a combination of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or PPA with $\text{Bi}(\text{OTf})_3$ in dichloromethane was the most efficient promoter for this type of transformation and preferentially delivered the β -anomer of **83**. In contrast, when either one of the catalysts was used separately, the reaction resulted in low yields and diminished selectivity.



In 2008, the same group developed $\text{Bi}(\text{OTf})_3$ /Montmorillonite K-10 catalysed Ferrier glycosylation, which produced the 3,4-unsaturated sialic acid derivatives with high β -selectivity. The latter compounds can be used to access new human parainfluenza virus type 1 (hPIV-1) inhibitors (eq. 17).²⁴



Iadonisi and co-workers discovered that glycosyl trichloro- and (*N*-phenyl)trifluoroacetimidates can be effectively activated with catalytic bismuth(III) triflate towards the *O*-nucleophiles (eq. 18).²⁵ Generally, the reactions proceeded under cryogenic conditions and were complete in less than 3 hours.



The choice of solvent seemed to be critical for this methodology, in which the best α -selectivity for perbenzylated donors was obtained in solvent mixtures containing toluene, DME and dioxane. While donors possessing a participating group gave the best β -selectivity in mixtures of dichloroethane and dioxane (Figure 1.3.1).

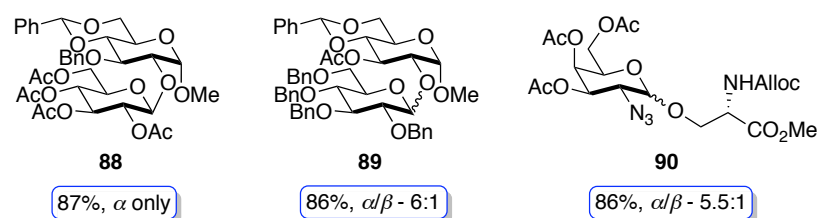
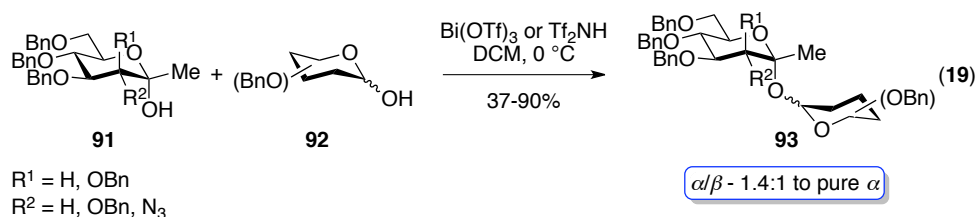


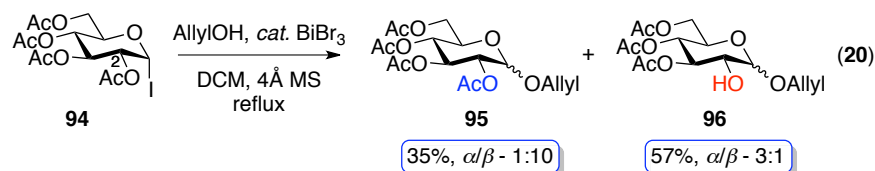
Figure 1.3.1: Selected Examples of Bi(OTf)₃ Catalysed O-Glycosylation Products

Yamanai's group has developed a convenient route for the synthesis of novel non-reducing saccharides with trehalose mimics (eq. 19).²⁶ The latter sugars display various biological activities such as suppression of osteoporosis progression and inhibition of fat cell enlargement.

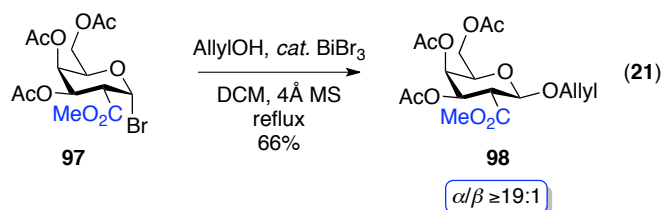


In the course of these studies, they compared various Lewis and Brønsted acids that were able to mediate the process, in which Bi(OTf)₃ and Tf₂NH outperformed most Lewis acids surveyed. Interestingly, the former was more beneficial in terms of yield, while the latter afforded slightly better α -selectivity.

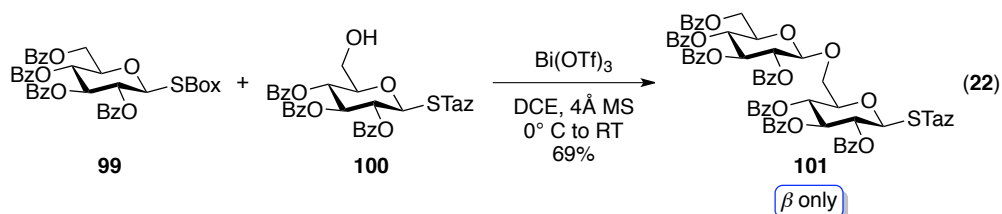
Iadonisi and co-workers have also reported a bismuth(III) bromide mediated anomeric activation of acetylated glycosyl iodides.²⁷ According to authors, the reaction outcome was highly dependent on the structural modification of the substrate. Hence, the peracetylated glycosyl iodides reacted with allylic alcohol with concomitant deprotection at the O-2 position (eq. 20).



In contrast, 6-deoxy sugars or sugars having benzoyl or methoxycarbonyl 2-*O*-participating groups underwent glycosidation without cleavage (eq. 21).



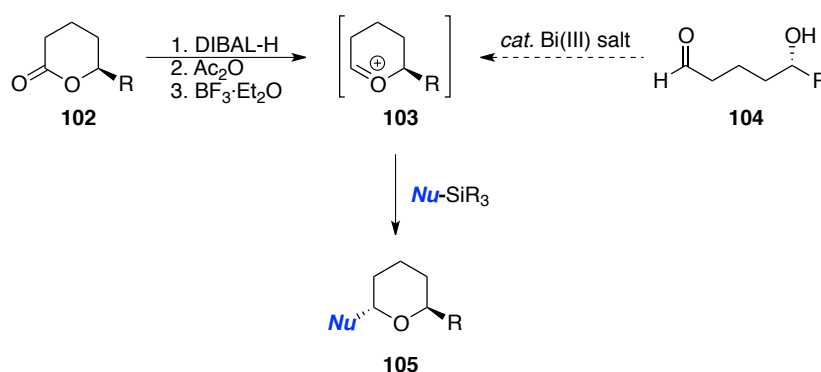
Demchenko *et al.* carried out a mechanistic study of the alkylation pathway for the activation of glycosyl thioimidates.²⁸ The authors have pursued a strategy that would allow an orthogonal activation of *S*-thiazolanyl (STaz) over *S*-benzoxazolyl (SBox) anomeric leaving groups. They found that the best promoter for the selective glycosylation was the stoichiometric Bi(OTf)₃, which allowed for the isolation of disaccharides in good yield and as the β -anomer only (eq. 22).



1.4 Intramolecular Etherification

Tetrahydropyrans (THPs) are structural motifs found in a variety of biologically active natural products such as polyether antibiotics, marine toxins, and pheromones.²⁹ Hence, the development of new methods for the stereodivergent construction of these systems is of great synthetic importance. Typically, control of the relative stereochemistry can be achieved in many ways, while the most general approach involves a three step procedure, involving: a) partial reduction of the lactone **102**; b) acylation or methylation of the intermediate lactol and c) addition of the nucleophile to the oxocarbenium ion **103**, formed by Lewis acid activation, e.g. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Scheme 1.4.1).³⁰

Scheme 1.4.1: *Synthesis of 2,6-Disubstituted Tetrahydropyrans via Oxocarbenium Intermediate **103***

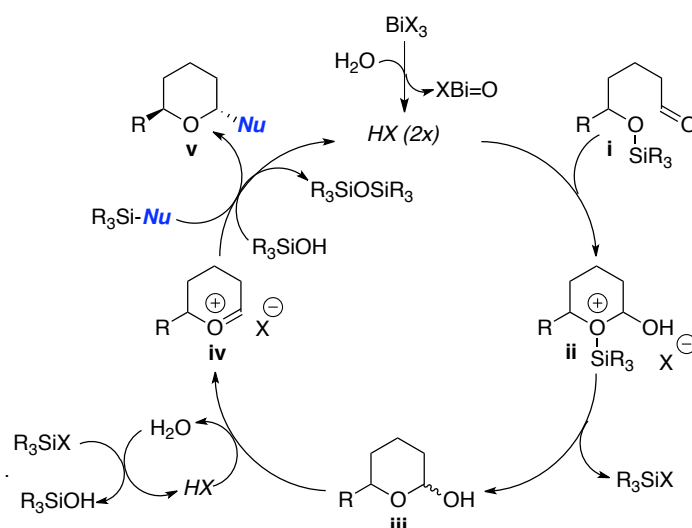


Based on the chemistry involving bismuth(III) mediated reductive etherification, the oxocarbenium ion **103** could be in principle generated under the reaction conditions. Subsequent nucleophile addition could provide the required tetrahydropyran in a straightforward fashion with concomitant formation of the C-O bond.

1.4.1 Tandem Two-Component Intramolecular Etherification

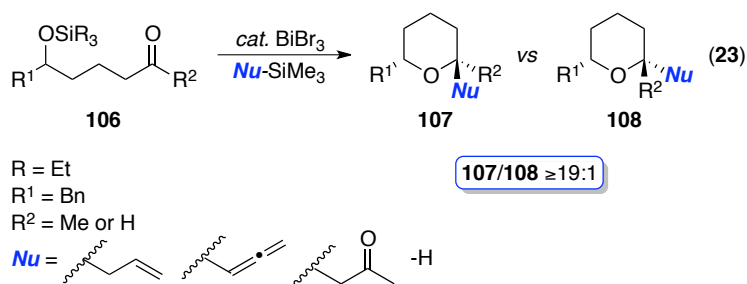
In 2003, Evans and co-workers proposed the mechanistic hypothesis for the two-component *intramolecular* etherification (Scheme 1.4.1.1).³¹ They reasoned that since bismuth(III) halides were known to undergo the hydrolysis in wet organic solvent to afford Brønsted acids,³² the latter could promote the formation of intermediate **ii** and subsequent *in situ* desilylation would afford lactol **iii**. The acid-catalysed dehydration of **iii** could then lead to the formation of the oxocarbenium ion **iv** and facilitate axial nucleophilic attack to furnish the cyclic ether **v**.

Scheme 1.4.1.1: *Mechanistic Proposal for the Two-component Intramolecular Etherification*

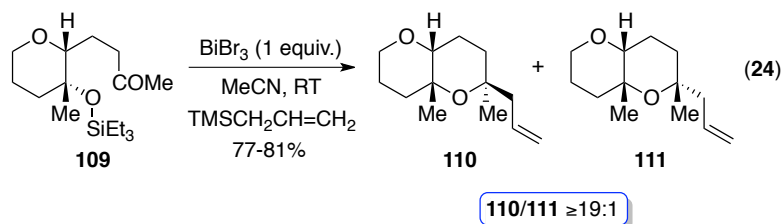


Initial results showed that the nature of bismuth(III) halide was unimportant for both efficiency and selectivity (Cl ~ Br ~ I). However, while the selectivity was unaffected by the nature of the triorganosilyl ether, the efficiency of the reaction was found to be highly dependant on the rate of protodesilylation (TMS ~ TES > TBS >> TIPS).³³ The study demonstrated that δ -triethylsilyloxy substituted aldehydes and ketones **106** served as substrates for the etherification reaction (eq. 23). Remarkably, the two-component coupling reactions with carbon nucleophiles furnished the *trans*-diastereoisomer of the pyran. On the other hand, the reductive coupling with Et₃Si-*H*

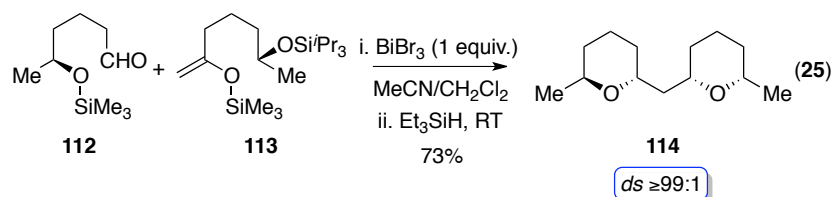
afforded the *cis*-THP diastereoisomer, consistent with the axial addition of the hydride nucleophile.³⁴



The developed methodology was extended to the formation of adjacent *bis*-tertiary ethers with very high stereoselectivity (eq. 24). The stereochemical outcome could be explained by the Woerpel model,³⁴ which predicted that the 4-alkoxy substituent would adopt a pseudoaxial orientation in the transition state, thereby favouring the *trans*-addition of the allylsilane.

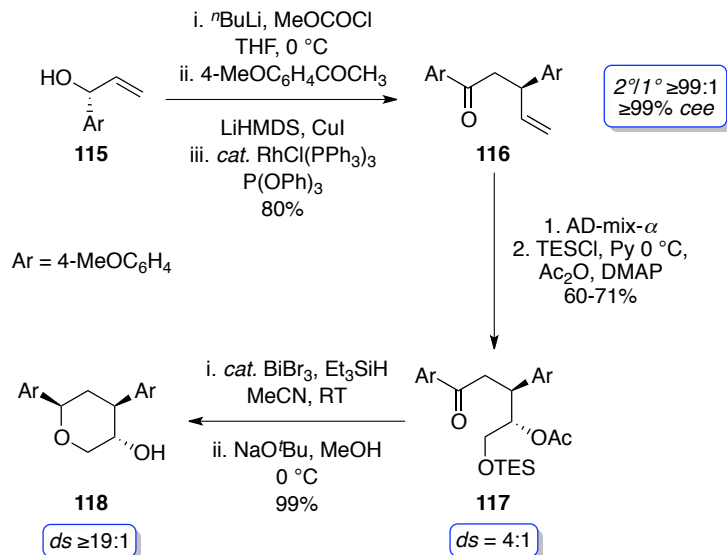


The synthetic utility of the transformation was highlighted in the sequential two-component reaction that involved an *intermolecular* addition followed by an *intramolecular* reductive etherification (eq. 25). Reaction of aldehyde **112** with excess of the trimethylsilyl enol ether **113** installed the *trans*-2,6-disubstituted tetrahydropyran, which upon addition of triethylsilane promoted the reductive etherification to afford *bis*-tetrahydropyran **114** in 73% yield and excellent diastereoselectivity.



The strategy for the preparation of tetrahydropyrans was used in the expedient route to (–)-sugiresinol by Evans and Leahy (Scheme 1.4.1.2).³⁵ Formation of the allylic carbonate from **115**, followed by *in situ* rhodium(I)-catalysed allylic alkylation afforded the β -substituted ketone **116** in 80% yield ($2^\circ/1^\circ \geq 99:1$, $\geq 99\%$ *cee*). Sharpless asymmetric dihydroxylation, followed by a one-pot differential protection, led to the cyclisation precursor **117** in 60–71% yield over two steps as a 4:1 mixture of diastereoisomers. The reductive etherification of **117** using bismuth(III) bromide and triethylsilane, succeeded by *in situ* deprotection of the acetyl group, afforded the (–)-sugiresinol dimethyl ether **118** in 99% yield and $\geq 19:1$ diastereoselectivity.

Scheme 1.4.1.2: (–)-Sugiresinol Synthesis via Rhodium(I)-Catalysed Allylic Alkylation and Bismuth(III)-Catalysed Intramolecular Reductive Etherification



Hinkle *et al.* investigated effect of various π -nucleophiles on the diastereoselectivity of BiBr₃ mediated cyclisation-addition reaction (eq. 26, Table 1.4.1.1).³⁶ They have showed that the diastereocontrol of the reaction decreases with

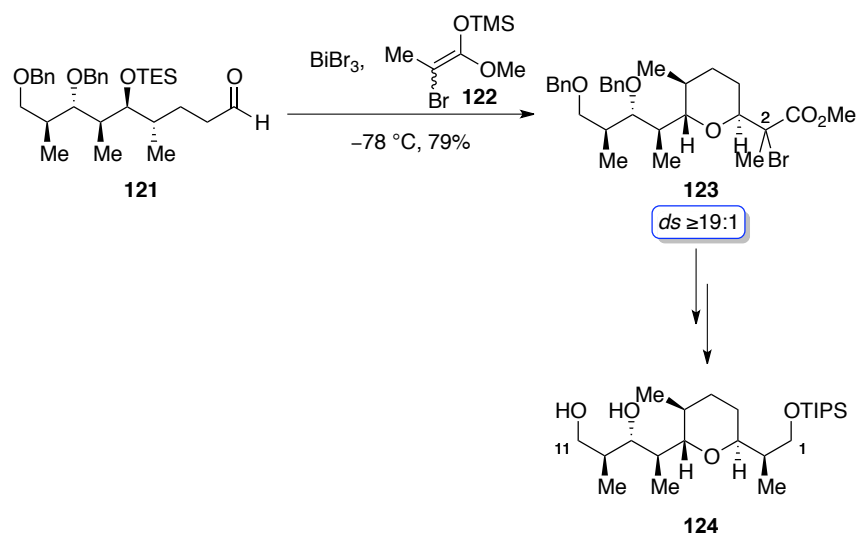
an increase of the π -character of the nucleophile and proposed that the transformation proceeds under the kinetic control.

Table 1.4.1.1: *Diastereoselectivity of Cyclisation-Addition Reaction of π -Nucleophiles*

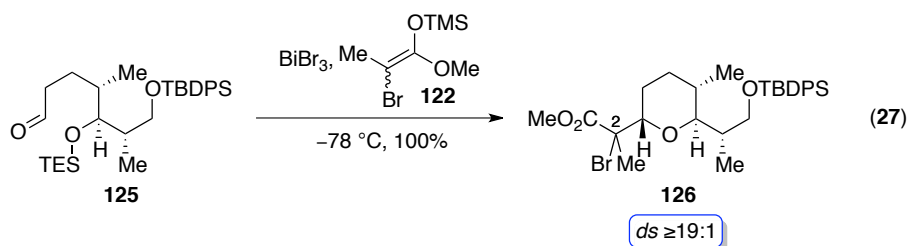
(26)

Nucleophile	Product, <i>trans/cis</i>	π -Nucleophilicity parameter, <i>N</i>
	99:1	1.79
	32:1	5.31
	5-6:1	~8.5

Guindon and co-workers successfully applied the tandem two-component etherification in the synthesis of the C1-C11 fragment of zincophorin **124** (Scheme 1.4.1.3).³⁷ The reaction of the advanced aldehyde **121** with enoxysilane **122** in the presence of bismuth(III) bromide afforded **123** as a 1:1 mixture of epimers at C2 with excellent *anti/syn* selectivity and 79% yield.

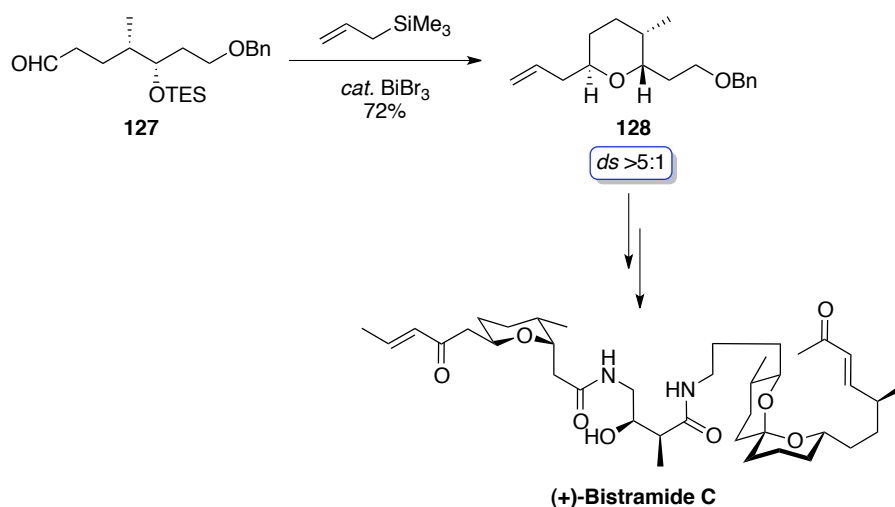
Scheme 1.4.1.3: Synthesis of the C1-C11 Fragment of Zincophorin

In the subsequent evaluation of the bidirectional approach towards the synthesis of zincophorin, Guindon *et al.* successfully showcased a pivotal BiBr₃ catalysed cycloetherification/addition strategy (eq. 27).³⁸ Similarly to their previous report, the reaction of **125** with **122** smoothly afforded the cyclic ether **126** in quantitative yield with excellent stereocontrol ($ds \geq 19:1$). Although the product was epimeric at C2, it was of little consequence since both isomers converge into one intermediate in the successive step.



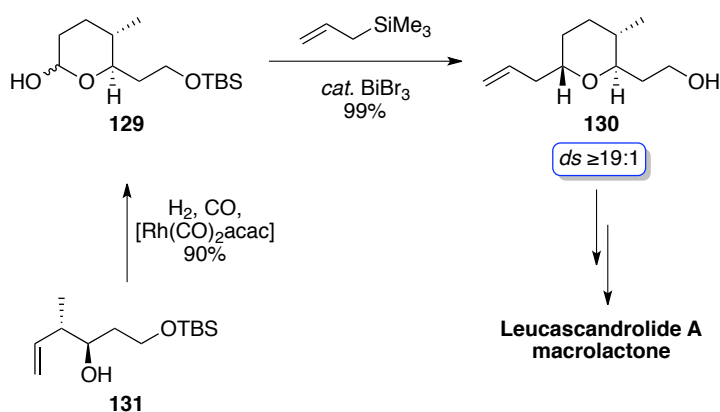
Wipf and Hopkins took the advantage of the tandem etherification-allylation for the preparation of the functionalised *trans*-substituted tetrahydropyran ring **128** in the course of total synthesis of (+)-bistramide C (Scheme 1.4.1.4).³⁹ The transformation was accomplished using the catalytic bismuth(III) bromide and allylsilane in 72% yield and with moderate stereocontrol ($ds > 5:1$).

Scheme 1.4.1.4: *Tandem Etherification-Allylation in the Preparation of trans-Substituted Tetrahydropyran Ring 128*



Interestingly, Floreancig *et al.* reported the formation of tetrahydropyran **130**, which is diastereomeric to **128**, albeit with higher stereoselectivity and yield (Scheme 1.4.1.5).⁴⁰ Hydroformylation of allylic alcohol **131** using $[\text{Rh}(\text{CO})_2\text{acac}]$ to furnish lactol **129** and subsequent allylation in the presence of BiBr_3 afforded **130** with $\geq 19:1$ stereocontrol and in quantitative yield.

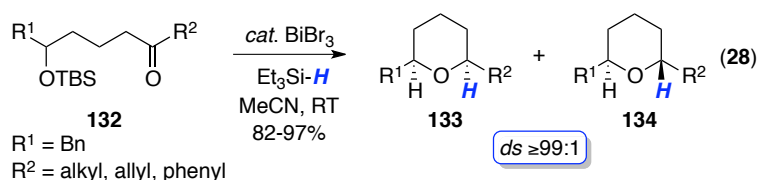
Scheme 1.4.1.5: *Preparation of trans-Tetrahydropyran 130 via the Lactol Intermediate 129*



According to authors, the reaction proceeded through an isolable bridged bicyclic acetal, resulting from the addition of the silyloxy group to the intermediate oxocarbenium ion, followed by an allyl group installation. This procedure permitted

a direct nucleophilic substitution of lactols with high yield and selectivity without the need to utilise low temperatures.

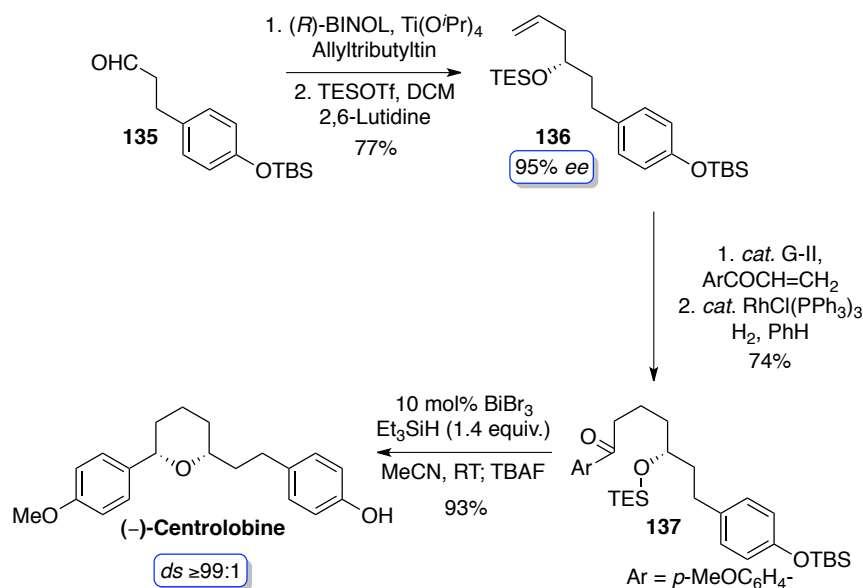
Evans and co-workers have extended the scope of BiBr₃ catalysed two-component etherification to a series of *tert*-butylsilyloxy ketones for the construction of *cis*-2,6-disubstituted tetrahydropyrans (eq. 28).⁴¹



The *intramolecular* reductive etherification reaction was shown to be highly tolerant to a wide array of substituents. Useful substrates included the aryl, α -branched alkyl, alkyl halide and those with alkene pendant groups, β -keto esters and hydroxymethyl derivatives. Remarkably, all examples exhibited excellent diastereoselectivities favouring the *cis*-2,6-disubstituted tetrahydropyrans ($ds \geq 99:1$).

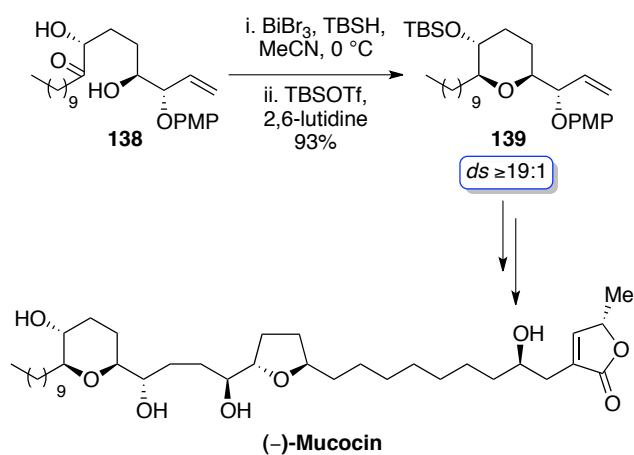
The stereoselective preparation of the *cis*-2,6-disubstituted tetrahydropyrans provided an expeditious route to the antibiotic (–)-centrolobine A (Scheme 1.4.1.6). Keck allylation of the aldehyde **135** (95% *ee*), followed by protection of the resulting secondary alcohol afforded triethylsilyl ether **136** in 77% overall yield. Cross-metathesis using Grubb's 2nd generation catalyst and chemoselective reduction with Wilkinson's catalyst furnished the aryl ketone **137** in 74% yield for 2 steps. The reaction of δ -triethylsilyloxy aryl ketone **138** with bismuth tribromide and triethylsilane at room temperature, succeeded by *in situ* removal of the TBS protecting group afforded (–)-centrolobine in 93% yield and excellent diastereocontrol.

Scheme 1.4.1.6: *Stereoselective Synthesis of (–)-Centrolobine Using the Intramolecular Reductive Etherification*



(–)-Mucocin is a potent antitumour agent isolated from leaves of *Rollinia mucosa* that exhibits exquisite selectivity in the inhibition of A-549 (lung cancer) and PACA-2 (pancreatic cancer) solid tumour lines with very high potency. The *intramolecular reductive etherification* of ketone **138** was used as a key step to construct the functionalised tetrahydropyran fragment of this natural product (Scheme 1.4.1.7).⁴²

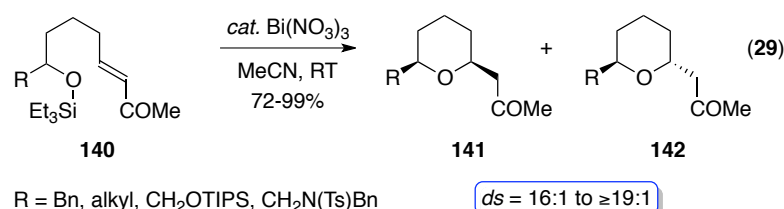
Scheme 1.4.1.7: *Application of the Intramolecular Reductive Etherification in the Total Synthesis of (–)-Mucocin*



Treatment of the functionalised ketone **138** with *tert*-butyldimethylsilane in acetonitrile at 0 °C and subsequent protection of free hydroxyl group in one pot afforded tetrahydropyran **139**, with the crucial 2,6-*cis* substitution pattern, in excellent yield and with high selectivity.

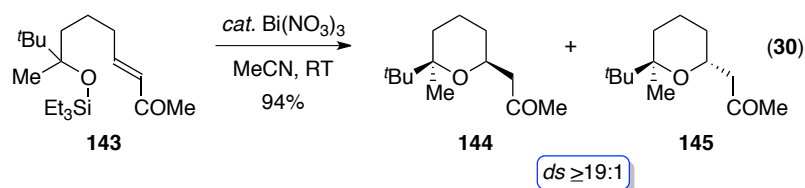
1.5 Synthesis of Cyclic Ethers *via* the Oxa-Conjugate Addition Reaction

Despite substantial progress made in the base-catalysed intramolecular *oxa*-conjugate addition of alkoxides, the Brønsted acid variant of this transformation remained highly underdeveloped.^{43,44} In a program directed towards the exploration of the synthetic utility of bismuth(III) salts, Evans and Andrews examined the application of the *intramolecular oxa*-conjugate addition of tethered trialkylsilyloxy substituted α,β -unsaturated ketones **140** for the stereoselective construction of the *cis*-2,6-disubstituted tetrahydropyrans **141** (eq. 29).⁴⁵



Optimisation studies suggested that bismuth(III) nitrate was the best catalyst for this type of transformation in terms of both yield and selectivity. The developed method was applied to various tethered triethylsilyloxy substituted α,β -unsaturated ketones and showed a remarkable generality in scope. Thus, high diastereoselectivities and yields were observed for substrates with α - and β -branching, TIPS or Bn protected ethers, carboxylates and masked amines. Furthermore, the synthetic utility of the transformation was highlighted by the application of the reaction conditions to the challenging tertiary triethylsilyl ether **143** (eq. 30). Treatment of the latter with 20 mol% of bismuth(III) nitrate

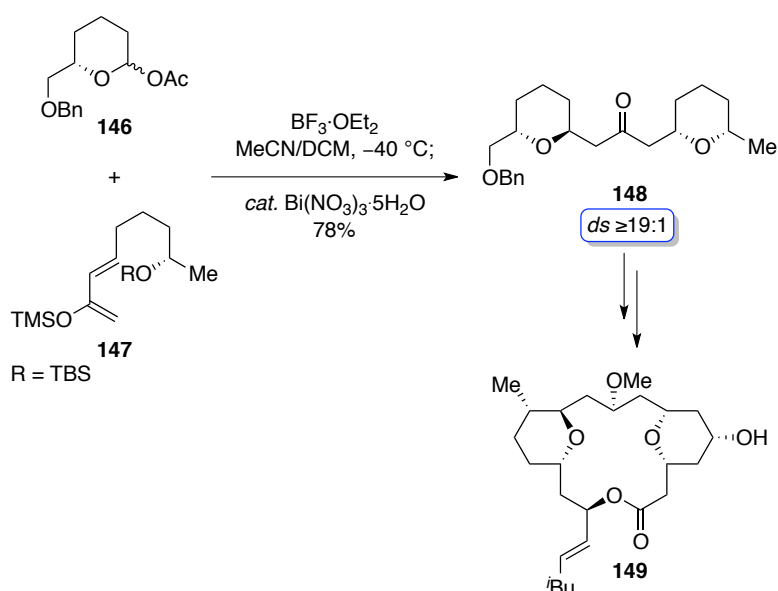
pentahydrate, furnished the tetrahydropyrans **144/145** in 94% yield, with $\geq 19:1$ diastereoselectivity favouring **144**.



This study provided a mild and efficient method for the highly stereoselective construction of the *cis*-2,6-disubstituted tetrahydropyrans using the secondary and tertiary alcohol nucleophiles. Additionally, it was shown that water, incorporated in the salt as a hydrate, was important in facilitating the reaction and that Brønsted acid rather than the bismuth(III) salt was actually responsible for the catalysis.

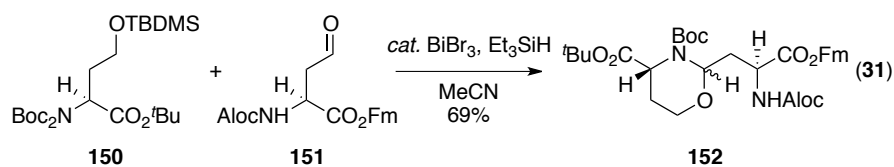
The bismuth(III)-catalysed *oxa*-conjugate addition was used by Evans and Andrews as part of a multi-component transformation in the asymmetric synthesis of (+)-leucascandrolide A macrolactone **149** (Scheme 1.5.1).⁴⁶

Scheme 1.5.1: *Bismuth(III) Catalysed Two-Component Etherification/Oxa-Conjugate Addition Reaction*



The non-adjacent *bis*-THP core **148** was obtained in 78% yield and with excellent diastereocontrol ($ds \geq 19:1$) using a two component etherification/*oxa*-conjugate addition reaction. The dual Lewis and Brønsted acid catalysis was crucial to effect this type of sequential process.

During the preparation of the ether bridged *bis*-amino acids, Tabor and co-workers observed the formation of the cyclic 1,3-tetrahydrooxazine **152** (eq. 31).⁴⁷ The transformation was likely to occur *via* hydrolysis of the one of nitrogen's *tert*-butyl carbamate groups and subsequent *intramolecular* attack of NHBoc on the oxocarbenium ion leading to the cyclic 1,3-tetrahydrooxazine **152**.

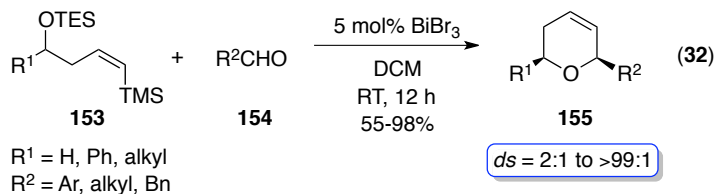


1.6 Etherification *via* a Tandem Processes

In 2006, Hinkle and Lian showed that catalytic BiBr₃ can mediate a tandem addition/silyl-Prins cyclisation reaction for the formation of *cis*-2,6-disubstituted dihydropyrans.⁴⁸ The main advantage of the developed methodology was the utilisation of extremely mild conditions offered by bismuth(III) bromide, which do not require the use of strictly anhydrous solvents or low temperatures.

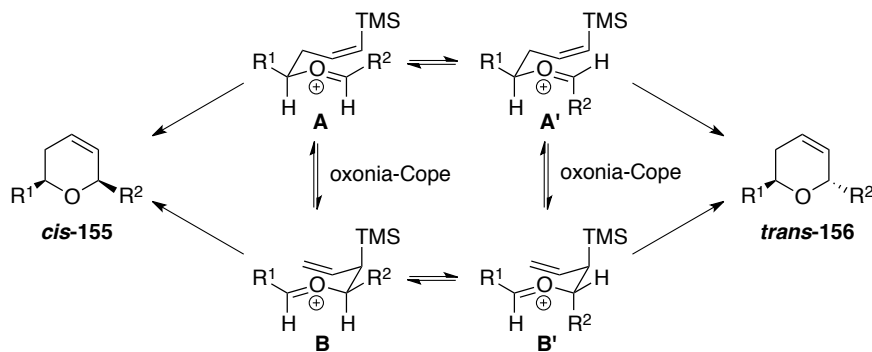
The reaction effectively proceeded with a range of benzyl or alkyl TES protected homoallylic silanols **153** and various aromatic, benzylic and aliphatic aldehydes **154** (eq. 32). Closer examination of the stereoselectivity indicated a strong dependence on the electronic properties of aldehydes employed. Thus, electron-deficient and aliphatic aldehydes afforded the cyclisation products in good-to-excellent yield and selectivity. However, the use of electron rich aromatic

aldehydes led to a decrease in yield as well as selectivity ($ds = 2\text{-}3\text{:}1$). It was showed that *trans*-dihydropyrans were actually kinetic products and the preference for them was a result of both steric and electronic factors.



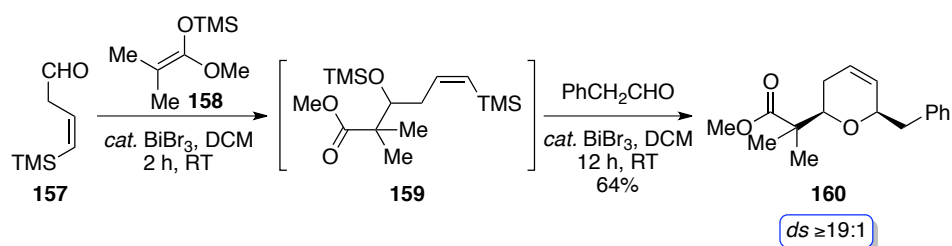
The observed *cis*-stereoselectivity could be rationalised by the formation of (*E*)-oxocarbenium ion **A** in which R^1 and R^2 adopted the pseudoequatorial positions to minimise the diaxial interactions, whilst the TMS moiety is oriented axially and allowed greater stabilisation of the cation that developed β to the silane (Scheme 1.6.1). A [3,3] sigmatropic oxonia-Cope rearrangement of **A** could then provide the oxocarbenium ion **B**.

Scheme 1.6.1: Possible Intermediates in the Silyl-Prins Cyclisation



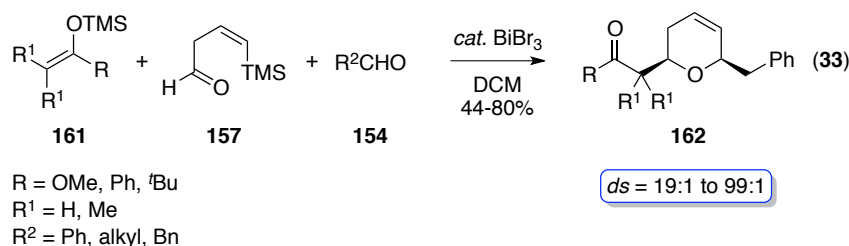
The attack of π -electrons on the oxocarbenium carbon *via* either **A** or **B** and subsequent desilylation would then provide the *cis*-dihydropyran **155**. Alternatively, formation of the stereoisomeric (*Z*)-oxocarbenium ion (**A'**) would afford an alternative pathway and lead to the corresponding *trans*-product **156**.

The authors demonstrated that the combination of the silyl-Prins cyclisation and the Mukaiyama aldol reaction could provide an expedient route towards the functionalised *cis*-2,6-disubstituted dihydropyrans as evident from Scheme 1.6.2.

Scheme 1.6.2: Tandem Silyl-Prins/Mukaiyama Aldol Reaction

The Mukaiyama aldol reaction between β,γ -unsaturated aldehyde **157** and methyl β,β -dimethylketenetrimesyl acetal **158**, in the presence of the catalytic amount of BiBr₃, furnished the intermediate **159**. The addition of phenylacetaldehyde and further 10 mol% of BiBr₃ afforded the functionalised dihydropyran **160** in a 64% overall yield as a single diastereoisomer.

This multi-component transformation was investigated further and extended to various silyl enol ethers **161** (eq. 33).⁴⁹

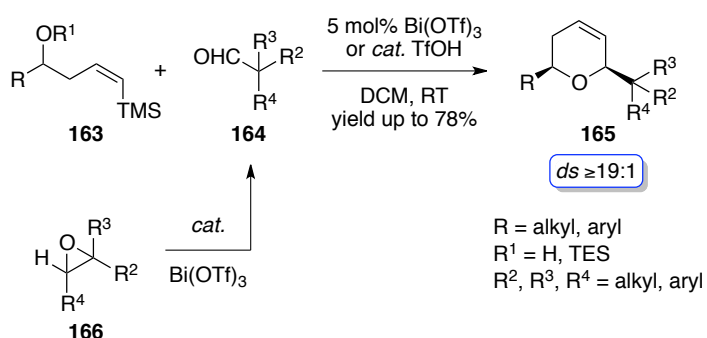


Generally, the reaction required a slight excess of the nucleophile **161** and proceeded smoothly with a wide array of electronically and sterically diverse aldehydes. In all cases excellent diastereoselectivities (up to 99:1) were observed as well as good yields (44-80%). The ability to use β,β -unsubstituted enol ethers as nucleophiles is remarkable, since the resulting products possess enolisable hydrogens α - to the carbonyl moiety.

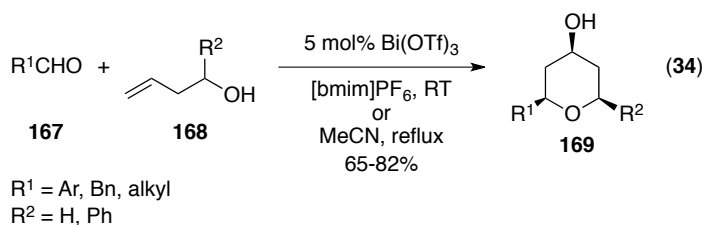
In 2011, Lambert, Hinkle and co-workers expanded the scope of the one-pot tandem addition/silyl-Prins reaction by exploiting an *in situ* bismuth(III) mediated epoxide rearrangement to give aldehyde electrophiles.⁵⁰ Additionally, they reinvestigated the role of bismuth(III) triflate in the transformation. It was found that

the initially occurring Lewis acid/base interaction between the substrate and $\text{Bi}(\text{OTf})_3$ afforded a catalytic quantities of TfOH . The latter Brønsted acid then acted as the active catalyst and promoted rearrangement of epoxide **166** to aldehyde **164** and subsequently mediated the multistep sequence leading to dihydropyran **165** (Scheme 1.6.3).

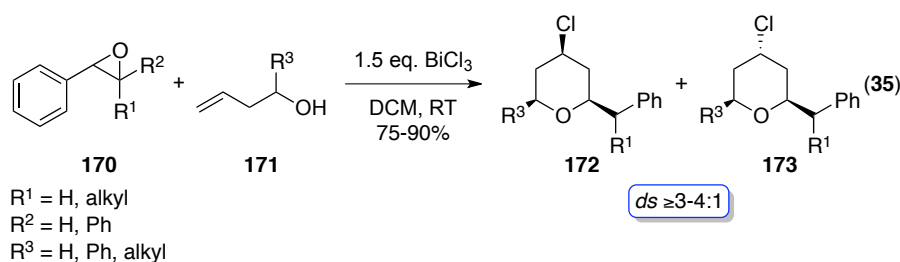
Scheme 1.6.3: $\text{Bi}(\text{OTf})_3$ Mediated Synthesis of Dihydropyrans



Prins cyclisation is a convenient and rapid way to access polysubstituted tetrahydropyrans (eq. 34). Several groups have developed the bismuth(III) triflate catalysed stereoselective Prins cyclisation reaction. The efficiency of the transformation was shown to be solvent dependent. Murty *et al.* demonstrated that the reaction could be carried out at room temperature in an ionic liquid,⁵¹ whereas Sreedhar and co-workers used refluxing acetonitrile.⁵² The latter group has also reported the Prins reaction between styrenes and paraformaldehyde to produce the corresponding 1,3-dioxanes.



The Murty group reported the development of a Prins-type cross-cyclisation reaction of epoxides with homoallylic alcohols mediated by bismuth(III) chloride (eq. 35).⁵³



The methodology allowed for the synthesis of di- and trisubstituted tetrahydropyrans favouring the all *cis*-stereoisomer as the major product. The reaction was believed to proceed through an epoxide opening mediated by bismuth(III) chloride, which would generate an electrophile, followed by the addition of alcohol and subsequent Prins cyclisation.

In 2001, the first bismuth(III) triflate catalysed stereoselective *intramolecular* Sakurai cyclisation (IMSC) of homoallylic alcohols was reported by Marko *et al.*⁵⁴ The developed procedure granted a novel route to the previously inaccessible tetrahydropyrans, which would otherwise require utilisation of the functionalised aldehydes, *i.e.* having α -alkoxy substitution and unreactive in IMSC condensation (eq. 36, Figure 1.6.1). Notably, when the cyclisation was carried out in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, a significant amount of desilylated starting material was obtained that showcased the unique and mild reaction conditions offered by bismuth(III) salts.

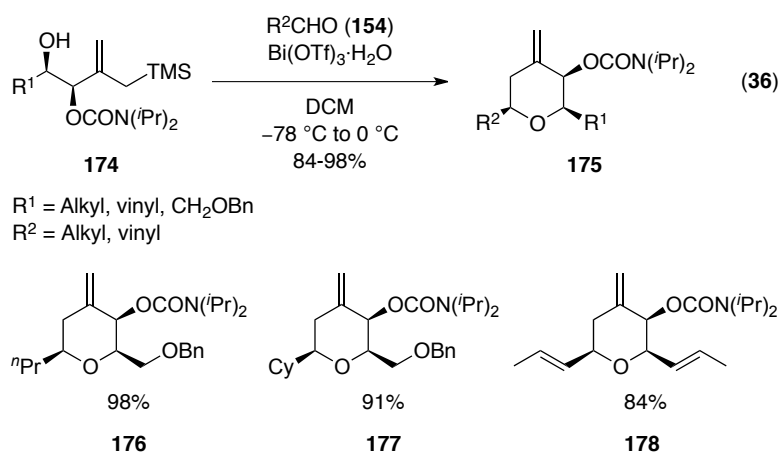
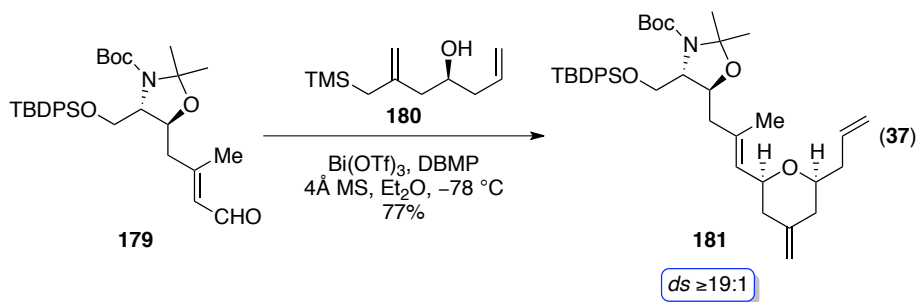


Figure 1.6.1: Selected Examples of Bi(OTf)_3 Catalysed IMSC of Homoallylic Alcohols

The IMSC reaction was applied in the synthetic studies towards (-)-zampanolide by Porco Jr. and co-workers.⁵⁵ They found that the condensation of the highly functionalised aldehyde **179** with **180** in the presence of 1.5 equiv. of Bi(OTf)₃ combined with 2,6-di-*tert*-butylpyridine afforded the 2,6-disubstituted *exo*-methylene pyran **181** as a single diastereoisomer in 77% yield (eq. 37).



Yadav and co-workers described a multi-component one-pot bismuth(III) triflate catalysed Prins-Ritter reaction of homoallylic alcohols, aldehydes and nitriles (eq. 38).⁵⁶ The reaction was shown to proceed with aliphatic and aromatic alcohols as well as diverse aldehydes and nitriles (Figure 1.6.2). Remarkably, the transformation can be applied to ketones to afford spiro compounds. The diastereoselectivity of the cyclisation was consistently high and only the *cis*-diastereoisomer was obtained in each case.

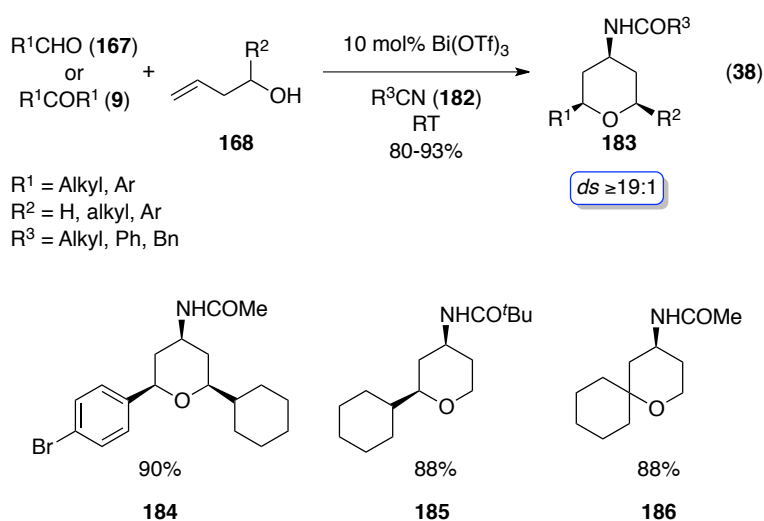


Figure 1.6.2: Selected Examples of the Prins-Ritter Reaction Catalysed by Bi(OTf)₃

Sabintha *et al.* reported a multi-component Sakurai-Prins-Ritter reaction mediated by bismuth(III) triflate (eq. 39).⁵⁷ Various aromatic and aliphatic aldehydes underwent the condensation with a range of nitriles with high efficiency (Figure 1.6.3).

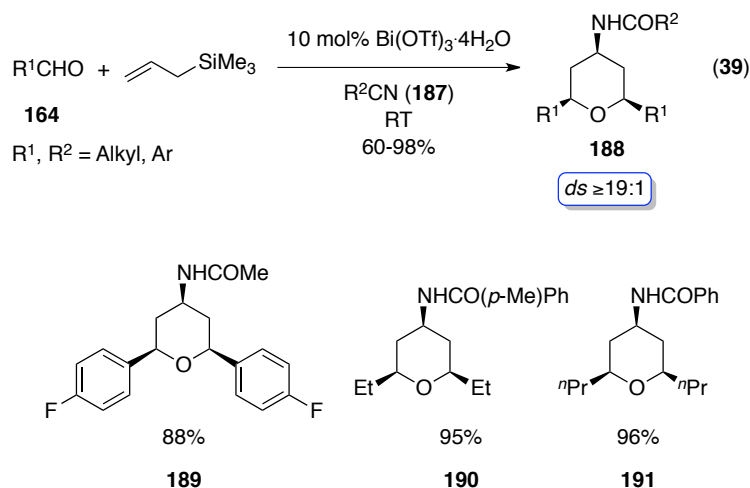
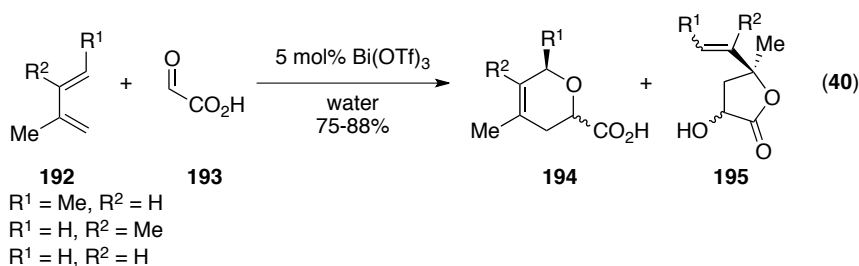


Figure 1.6.3: Selected Examples of the Sakurai-Prins-Ritter Reaction
Catalysed by Bi(OTf)_3

High yields were generally obtained and the reactivity of aliphatic aldehydes was shown to be higher than aromatic ones. The stereochemistry of tetrahydropyrans was established to be all-*cis* and one diastereoisomer was always obtained.

1.7 Bismuth(III) Mediated Hetero-Diels-Alder Reaction

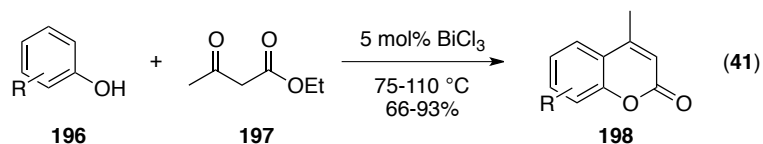
Dubac and co-workers showed that bismuth(III) triflate was able to activate the carbonyl compounds towards the reaction with dienophiles (eq. 40).⁵⁸



Yields of this transformation were generally high, however the *cis/trans* selectivity of the dihydropyran formed was very low. It was shown that the process suffered from the formation of the α -hydroxy- γ -lactone **195**, which was often acquired as the sole reaction product.

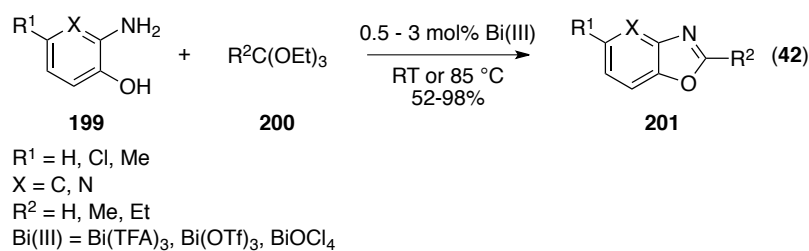
1.8 Cyclic Ether Synthesis *via* Condensation Reaction

De and Gibbs reported that bismuth(III) chloride could be an efficient catalyst for the Pechmann condensation reaction of phenols with β -ketoesters for the formation of 4-substituted coumarins (eq. 41).⁵⁹

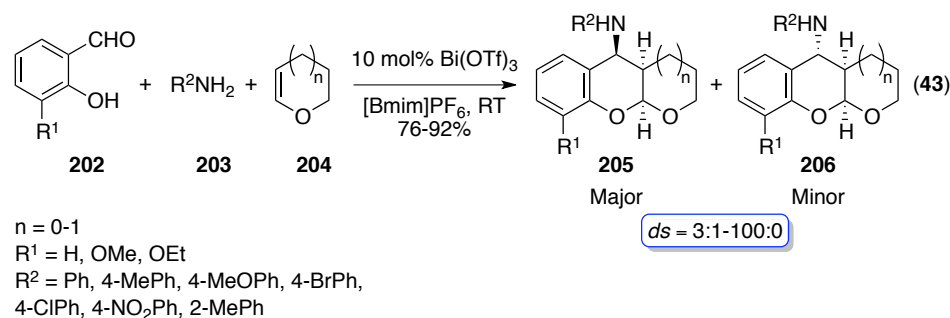


Samant and co-workers found a rate-accelerating effect of ultrasound on the Pechmann condensation of phenols and β -ketoesters mediated by BiCl_3 .⁶⁰ The synergetic effect of the ultrasound allowed the transformation to be conducted at room temperature in shorter reaction time and higher yields compared to the thermal variant. This group also reported similar reaction catalysed by $\text{Bi}(\text{NO}_3)_3$.⁶¹

Mohammadpoor-Baltork *et al.* have described a synthesis of various benzoxazoles and oxazolo[4,5-*b*]pyridines *via* the condensation of *o*-aminophenols and 2-amino-3-hydroxypyridines with orthoesters in the presence of catalytic Bi(III) salts (eq. 42).⁶² The authors showed that the reaction proceeded under mild conditions with good to excellent yields regardless of the source of bismuth(III) used.

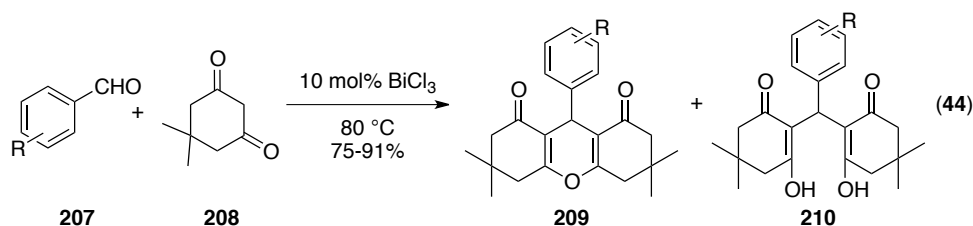


Yadav and co-workers developed a recyclable catalytic system for the diastereoselective synthesis of the *cis*-fused pyrano- and furanobenzopyrans (eq. 43).⁶³ The methodology allowed for the stereoselective preparation of various chromenes and chromanes, which are found in many naturally occurring bioactive molecules and possess a wide range of biological activities.



While the reaction proceeded in conventional organic solvents, the application of the ionic liquids allowed the catalyst to be reused up to four times with only a slight decrease in the activity.

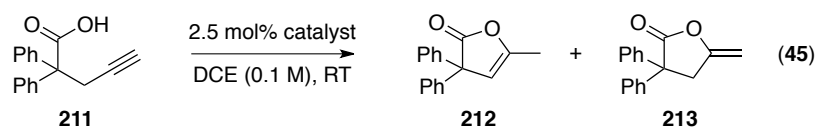
Li *et al.* have developed a route towards 1,8-dioxo-octahydroxanthenes.⁶⁴ Heterocycles containing the latter framework are widely used in dye and laser technologies. In addition, they show the important biological activities such as antibacterial, antiviral and anti-inflammatory. The aromatic aldehydes underwent a smooth condensation with an excess of 5,5-dimethyl-1,3-cyclohexanedione **208** in the presence of catalytic BiCl_3 to afford the xanthene derivatives in good to excellent yields (eq. 43). Interestingly, in the absence of the catalyst the reaction terminated during the formation of the intermediate **210**.



1.9 Cyclic Ethers Synthesis via Oxa-Addition Reaction to Unactivated π -Systems

Koneyama and co-workers reported that bismuth(III) triflate can catalyse *intramolecular* hydro-oxycarbonylation reaction of carboxylic acids and alkynes.⁶⁵ Initial findings showed that bismuth(III) salts have a unique reactivity profile when compared to other π - and Lewis acids. As seen from the Table 1.9.1, only borderline metal catalysts such as $\text{Fe}(\text{OTf})_3$ or $\text{Bi}(\text{OTf})_3$, which can interact with both heteroatoms and C-C multiple bonds, afforded the *endo*-lactone **212** as the cyclisation product (entries 6-9). In contrast, late transition metals, *e.g.* PdCl_2 and PtCl_2 , furnished the undesired 5-membered vinylidene-lactone **213** exclusively (entries 2 and 3).

Table 1.9.1: Screening of Catalysts for the Hydro-Oxycarbonylation (eq. 45)



Entry	Catalyst	Time (h)	Yield (212/213) (%)	Conv. (%)
1	$\text{Sc}(\text{OTf})_3$	24	n.r.	-
2	PdCl_2	22	67 (0/100)	67
3	PtCl_2	9	95 (0/100)	100
4	$\text{Ni}(\text{OTf})_2$	24	10 (0/100)	16
5	$\text{Cu}(\text{OTf})_2$	24	9 (0/100)	9
6	$\text{Fe}(\text{OTf})_3$	24	45 (100/0)	100
7	$\text{Bi}(\text{OTf})_3$	0.5	83 (100/0)	100
8	$\text{Bi}(\text{ClO}_4)_3$	0.5	79 (100/0)	100
9	$\text{Bi}(\text{BF}_4)_3$	0.5	52 (100/0)	100

Interestingly, substrates containing two terminal alkynyl and carboxylic moieties could undergo cyclisation into the spiro-lactone **214**. Whereas in systems

bearing two π -components, *e.g.* double and triple bond, the reaction proceeded chemoselectively with the alkyne moiety, albeit in moderate yield, to deliver **215** (Figure 1.9.1). Notably, a similar trend was observed with Au(I) catalyst.⁶⁶

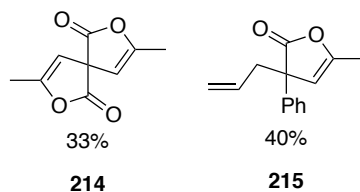
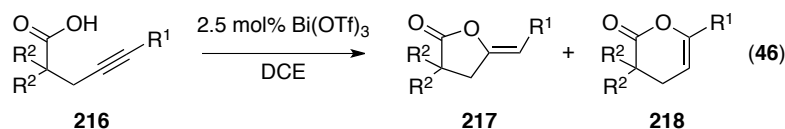


Figure 1.9.1: Selected Examples of $\text{Bi}(\text{OTf})_3$ Catalysed Hydro-Oxycarbonylation

The cyclisation of aromatic alkynes was also investigated (eq. 46, Table 1.9.2). In most cases, the formation of the six-membered lactone proceeded predominantly.

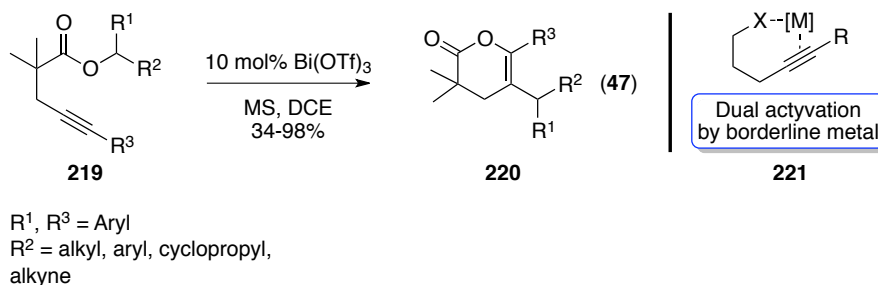
Table 1.9.2: Hydro-Oxycarbonylation of Disubstituted Alkynes (eq. 46)



Entry	Alkynyl carboxylic acid 216		Time (h)	Yield (217 + 218) (%)	Ratio (217 / 218)
	R^1	R^2			
1	Ph	Ph	3	95	28/72
2	4-MeOC ₆ H ₄	“	1.5	54	0/100
3	4-BrC ₆ H ₄	“	0.5	83	0/100
4	Ph	Me	0.5	92	12/88
5	4-MeOC ₆ H ₄	“	0.5	100	0/100
6	4-BrC ₆ H ₄	“	1.5	99	24/76

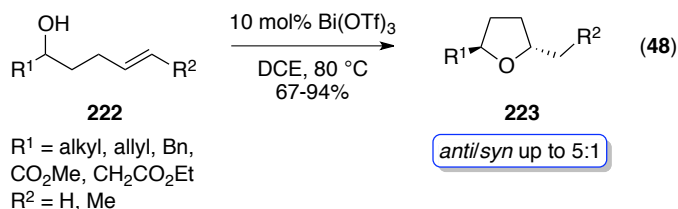
Although the exact role of bismuth was not determined, the authors proposed the dual activation of both carboxylic acid and alkyne by the bismuth(III) catalyst. Thus, the bismuth salts act as both σ - and π - acids, which is consistent with the previous findings in the field.⁶⁷

The same group developed the *intramolecular* hydro-oxycarbonylation reaction further and reported bismuth(III) triflate catalysed carbo-oxycarbonylation of alkynyl esters (eq. 47).⁶⁸



The authors hypothesised that the dual catalytic nature of bismuth could be used to bring two reaction centres into proximity (*e.g.* **221**) and facilitate the transformation. Among various catalysts, bismuth(III) triflate turned out to perform the best in terms of yield and the reaction time. Interestingly, triflic acid afforded only trace amounts of the desired product. This showed that the ability of Bi(OTf)_3 to release the acid upon hydrolysis did not play an important role in the transformation.

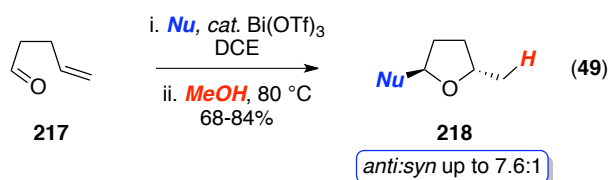
Lambert's group investigated the ability of bismuth(III) salts to mediate the multicatalytic processes.⁶⁹ In the course of the studies, they developed Bi(OTf)_3 -catalysed hydroxylation of unactivated olefins for the synthesis complex tetrahydrofuranyl products with good yield and diastereoselectivity favouring the *anti*-isomer (eq. 48).



Subsequently, the synthetic utility of the methodology was expanded by performing the nucleophilic addition/hydroxylation in one pot, both mediated by Bi(OTf)_3 (eq. 49, Table 1.9.3). The developed methodology allowed one-pot

Mukaiyama aldol/hydroxylation and Sakurai addition/hydroxylation reactions to be performed in good yield favouring the formation of *anti*-tetrahydrofurans, which are structurally relevant to natural products. In contrast to Koneyama's findings (*vide supra*), Lambert proposed that since the reactivity of Bi(OTf)₃ mirrored that of the triflic acid, the low-level release of the latter could act as an active catalyst in their system. This assumption was proved by showing that triflic acid catalysed hydroxylation with the same efficiency as Bi(OTf)₃.

Table 1.9.3: Selected Examples of Bi(OTf)₃ Catalysed Multicatalytic Synthesis of Complex Tetrahydrofurans (eq. 49)



Entry	Nucleophile	Substrate	Product	Yield (%)	<i>ds</i>
1				76	2.2:1
2				70	4:1
3	TMSCN			75	7.6:1

1.10 Conclusion

Since Komatsu's original report that BiBr_3 can be used as a catalyst for reductive etherification a great deal has been learned about the scope and limitation of this methodology. Recent advances in the field have provided the mechanistic insight and suggested new *inter*-, *intra*- and multi-component transformations for the formation of important derivatives for the target-oriented synthesis. Furthermore, it was showed that bismuth salts can act as both σ - and π - Lewis acids and play a vital role in the activation of C-C unsaturated bonds towards the heterofunctionalisation. Future work in this area will broaden the use of bismuth(III) salts as environmentally benign reagents and provide new ways for the synthesis of complex targets.

1.11 References

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- ² Wurtz, A. *Ann. Chem.* **1856**, 46, 222.
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Chapter 2

Diastereoselective Synthesis of Protected *syn*-1,3-Diols via the Intramolecular Conjugate Addition of Hemiacetal Nucleophiles**2.1 Introduction to the Polyene Macrolides**

Polyene macrolides are a large group of natural products that have diverse biological activity.¹⁻³ Several members of this class (e.g. amphotericin B, nystatin, and pimaricin) are effective as antifungal agents and have broad use in medicine.⁴ Most of these compounds share the common structural features such as a conjugated polyene ranging from three to seven double bonds in length, and more importantly, a polyol section made up of a sequence of 1,2-, 1,3- and 1,4-diols, with 1,3-diols being the most prevalent (Figure 2.1.1).

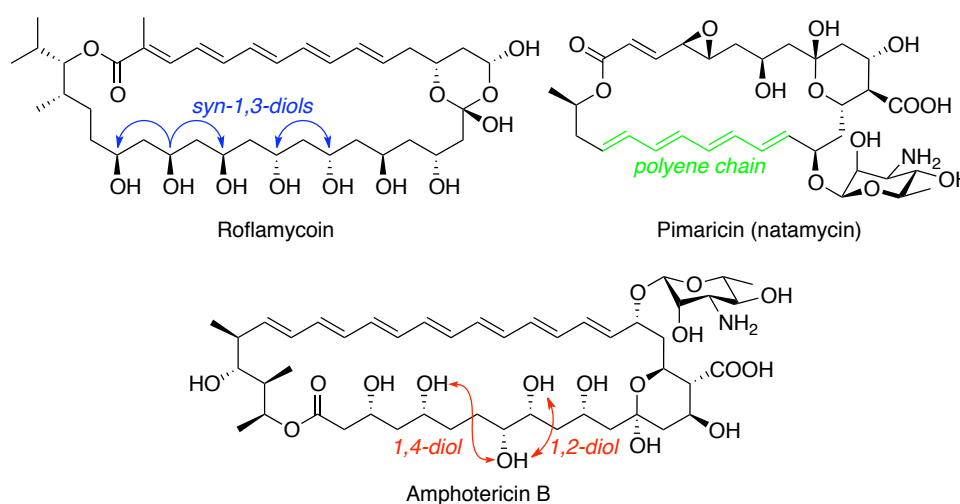
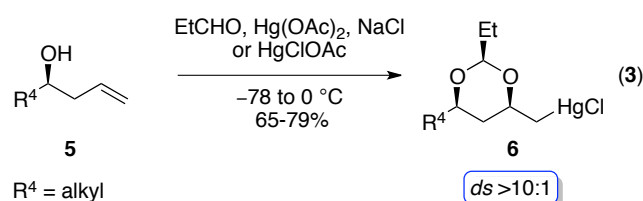
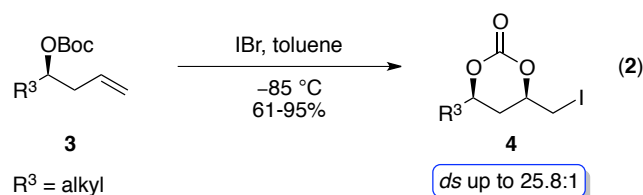
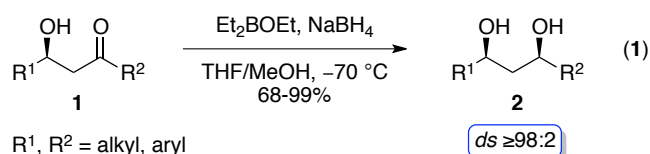


Figure 2.1.1: Structures of the Selected Polyene Macrolide Antibiotics

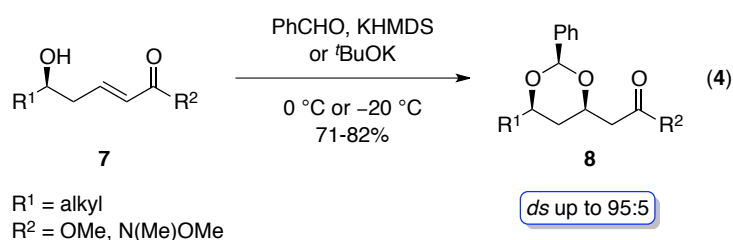
2.2 Background of 1,3-Polyol Syntheses

The construction of 1,3-polyols, especially *syn*-1,3-diols of the polyacetate (rather than the polypropionate type) is a continuing synthetic challenge.⁵ A number

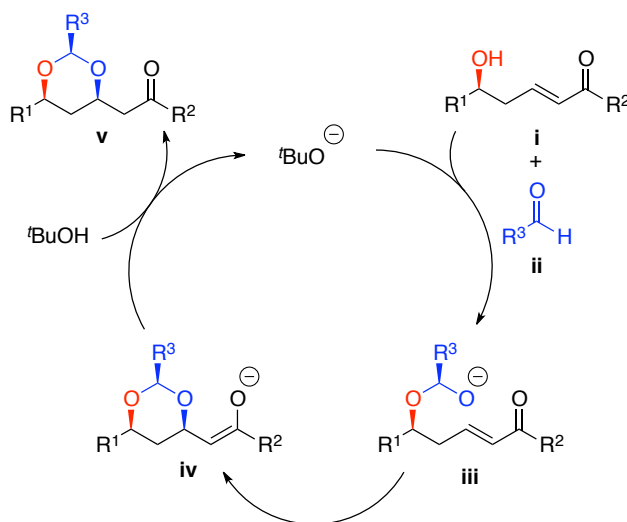
of methods have been developed to create this dioxygen relationship and the most important among them are β -hydroxy ketone reduction (eq. 1),⁶ electrophile-induced *intramolecular* addition of oxygen nucleophiles to homoallylic alcohols (eq. 2)⁷ and oxymercuration of homoallylic alcohol-derived hemiacetals (eq. 3).⁸



While most of these transformations deliver the desired products with good yield and stereocontrol, many of them suffer from the need to utilise cryogenic temperatures and/or toxic reagents. Although not lacking from the abovementioned drawbacks, the methodology developed by D. A. Evans and Gauchet-Prunet stands out as one of the most direct and convenient methods developed to date.⁹ In this context, the base mediated combination of aryl aldehyde with a δ -hydroxy α,β -unsaturated ester or amide delivers efficient 1,3-stereoiduction and provides the *syn*-1,3 protected diols in good yield (eq. 4).



The key features of this transformation are depicted in Scheme 2.2.1. The base mediated reaction of alcohol **i** with aldehyde **ii** affords the hemiacetal anion **iii**. Subsequent *intramolecular* Michael addition to the α,β -unsaturated system results in enol **iv**, which affords the protected *syn*-1,3-diol **v** after equilibration.



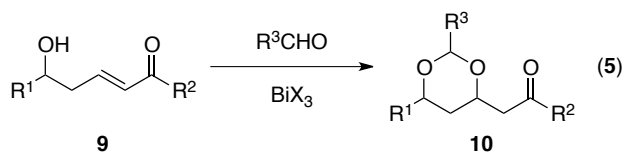
Scheme 2.2.1: Mechanism of the Base-Catalysed Intramolecular Conjugate Addition of the Hemiacetal-Derived Alkoxide Nucleophiles

Unfortunately, the scope of the abovementioned methodology is rather limited. Firstly, only aromatic aldehydes deliver the *syn*-1,3-diols with acceptable stereocontrol. In contrast, when isobutyraldehyde or acetaldehyde are employed, the *syn*- and the *anti*-diastereoisomers are formed in 1:1 ratio. Secondly, since Cannizzarro disproportionation¹⁰ sequesters the aromatic aldehyde, excessive stepwise addition of the latter and the base is needed to drive the reaction to completion. Thirdly, the choice of the electron-withdrawing groups on the alkene moiety is restricted to esters and amides. Consequently, oxidation state adjustments are necessary in order to employ these products in the subsequent steps of the target-oriented synthesis.^{11,12}

Thus, the development of the new methodology, which would allow the formation of the protected *syn*-1,3-diols, having the electron-withdrawing groups in the aldehyde and ketone oxidation state, could make the process more redox efficient¹³ and find wide synthetic application in the total synthesis.

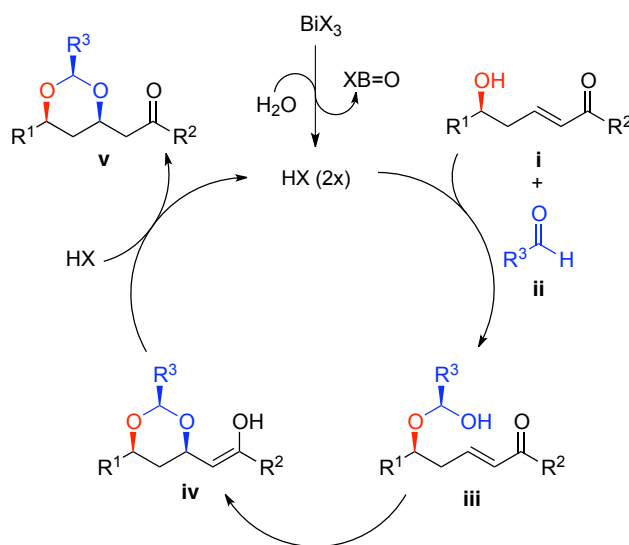
2.3 Mechanistic Proposal for the Bismuth(III) Mediated Construction of the Protected *syn*-1,3-Diols

On the basis of our previous studies in the field of bismuth(III) mediated reductive etherification¹⁴ and *oxa*-conjugate addition,¹⁵ we envisioned that it would be possible to take advantage of the unique bismuth(III) salts properties for the preparation of the protected 1,3-diols in the form of the cyclic acetals (eq. 5) (*vide supra*).



The plausible mechanistic details of this proposal are depicted in Scheme 2.3.1. Based on the previous findings by the Evans group^{14a} and others¹⁶ it is known that bismuth salts undergo hydrolysis in organic solvents due to the presence of trace amounts of moisture and afford a buffered acidic medium. The resultant Brønsted acid (HX) could activate aldehyde **ii** and in principle mediate the formation of hemiacetal **iii**. The latter could undergo an *intramolecular* conjugate addition and furnish the 1,3-protected diol **v** *via* the intermediacy of enol **iv**. The latter process could be mediated either by bismuth(III) salt, acting as a Lewis acid, or by HX *via* hydrogen bonding activation of carbonyl, as independently shown by Spencer¹⁷ and Evans.¹⁵ Moreover, assuming the reversibility of all mechanistic steps, the

thermodynamic reaction control could result in 1,3-stereoiduction and provide the *syn* relationship between the newly formed stereocentres.



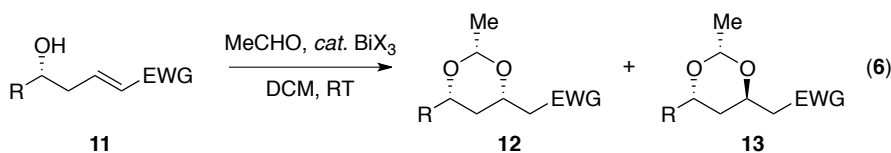
Scheme 2.3.1: *Proposed Catalytic Cycle for the Reaction Between the Homoallylic Alcohol **i** and the Brønsted Acid Activated Aldehyde **ii***

2.4 Reaction Optimisation for the δ -Hydroxy α,β -Unsaturated Ketones

For our preliminary studies, we elected to use substrates containing electronically different α,β -components. Table 2.4.1 shows the evaluation of various homoallylic alcohols, biased to unsaturated carbonyl derivatives, and the Brønsted acid sources in the two-component hemiacetal/*oxa*-conjugate addition reaction. Treatment of **rac-11a** with 5 equiv. of acetaldehyde and the catalytic bismuth(III) salt, which produced weak acid upon hydrolysis, did not provide any of the desired product (entry 1). In contrast, strong Brønsted acids performed with similar efficiency (entries 2-6). Whereas bismuth(III) nitrate pentahydrate as a source, afforded the required product **rac-12a** in the near quantitative 99% yield and excellent selectivity (*ds* \geq 19:1) (entry 2). Interestingly, the analogous process with nitric acid, acting as the active catalyst, provided the 1,3-dioxane **rac-12a** in a

significantly lower yield (entry 7).¹⁸ Thus, clearly illustrating the superiority of bismuth salts, which were able to modulate acid concentration *in situ*, over the conventional mineral acids.^{14a}

Table 2.4.1: *Optimisation of the Two-Component Hemiacetal/Oxa-Conjugate Addition Reaction (eq. 6)*



Entry ^a	Homoallylic alcohol		Acid source	Yield (%) ^b	ds <i>rac</i> - 12/13 ^c
	<i>rac</i> - 11 , R = Ph(CH ₂) ₂	EWG			
1	COMe	a	Bi(OAc) ₃	0	-
2	“		<i>Bi(NO₃)₃·5H₂O</i>	99	≥19:1
3	“		BiCl ₃	98	“
4 ^d	“		BiCl ₃	92	“
5	“		BiBr ₃	84	“
6	“		Bi(OTf) ₃	94	“
7 ^e	“		HNO ₃	34	“
8	“		BiI ₃	0	-
9	“		BiOCl	0	-
10	CO ₂ Me		Bi(NO ₃) ₃ ·5H ₂ O	0	-

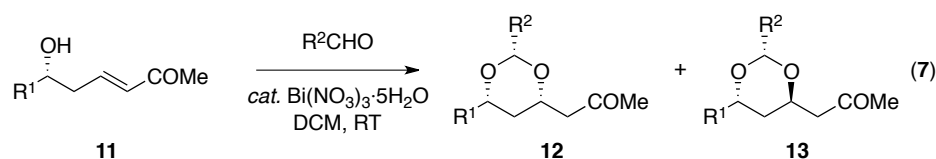
^aAll reactions were carried out on 0.5 mmol scale in DCM at room temperature using 10 mol% Bi(III) salt and 5 equiv. of the acetaldehyde for 16 hours. ^bIsolated yield. ^cDiastereomeric ratio determined by 500 ¹H MHz NMR analysis of crude reaction mixtures. ^d5 mol % of BiCl₃ has been used. ^eReaction was conducted with 20 mol % nitric acid.

The inactivity of bismuth(III) iodide could be explained by the disproportionation reaction of HI formed in the hydrolysis process (entry 8). While the addition of the BiOCl (the actual hydrolysis product of BiCl₃) afforded no product at all and served as further evidence that the transformation was Brønsted acid, but not Lewis acid catalysed (entry 9). Lastly, in contrast to the base-mediated

process, α,β -unsaturated esters were completely unreactive under our conditions (entry 10). This could be attributed to the lower nucleophilicity of the hemiacetal, which could not undergo *intramolecular* Michael addition, compared to the hemiacetal alkoxide anion, formed in the base-mediated process.

Further studies examined the scope of aldehydes able to participate in the process (eq. 7, Table 2.4.2). The reaction was shown to be very efficient with various linear and branched aliphatic aldehydes (entries 1-4). Notably, the aromatic counterparts were unreactive, which was associated with their lower electrophilic nature (entries 5, 6).¹⁹

Table 2.4.2: Aldehyde Scope for the Two-Component Hemiacetal/Oxa-Conjugate Addition Reaction (eq. 7, $R^1 = Ph(CH_2)_2$)



Entry ^a	Aldehyde, R ²		Yield (%) ^b	<i>ds rac-12/13</i> ^c
1	Me	a	99	≥19:1
2	ⁱ Pr	aa	98	“
3 ^d	^t Bu	ab	90	“
4	H	ac	98	“
5	Ph	ad	0	-
6	<i>p</i> -MeOPh	ae	0	-

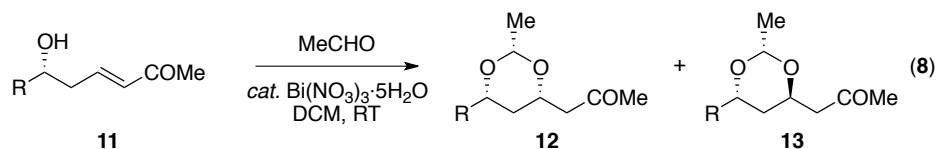
^aAll reactions were carried out on 0.5 mmol scale in DCM at room temperature using 10 mol% Bi(NO₃)₃ and 5 equiv. of the aldehyde for 18 hours. ^bIsolated yield. ^cDiastereomeric ratio determined by 500 MHz ¹H NMR analysis of crude reaction mixtures. ^dReaction time was 40 hours.

Based on results obtained, Bi(NO₃)₃ and acetaldehyde were designated as the optimum reagents, since this system afforded the highest yield and selectivity in the shortest period of time, and were used for the further studies.

2.5 Reaction Substrate Scope for the δ -Hydroxy α,β -Unsaturated Ketones

Having established the optimal conditions for the *syn*-1,3-dioxane formation, the reaction substrate scope was investigated. As outlined in Table 2.5.1, bismuth(III) nitrate efficiently catalysed the reaction of diverse δ -hydroxy α,β -unsaturated ketones with acetaldehyde. The transformation was quite general and excellent results were obtained with both linear and branched substrates (entries 1-9). Aromatic counterparts turned out to be less reactive, although they still delivered high yields and diastereoselectivities (entries 13-16). The reaction of *p*-methoxybenzyl alcohol **rac-11n** was accompanied by the acid mediated dehydration and formation of the diene as the only side product (entry 14). Interestingly, the reduced diastereoselectivity was observed in the case of alcohols **rac-11o** and **rac-11p**. This could be attributed to the lower nucleophilicity of the reacting alcohol and thus the greater kinetic character of the transformation. Remarkably, the *intramolecular* hemiacetal *oxa*-conjugate addition was also applicable to substrates containing protected heteroatom (entries 10-12), which implied that the methodology could be effective for applications in multistep synthesis, where protecting group strategy is important. It is noteworthy that silyl group migration/cyclisation was a major side reaction in the base catalysed variant of the transformation.²⁰ In our case, we observed only a trace amount (<5%) of silyl migration products from substrates **rac-11k** and **rac-11l** (entries 11 and 12). The reaction conditions were so exceptionally mild that the substrate containing a halogen atom (**rac-11d**) was readily tolerated, what was not achievable in the base-catalysed variant of this transformation due to the competing β -elimination (entry 4). Lastly, the operational simplicity of the methodology did not require the exclusion of air or moisture and could be conducted on a large scale with similar efficiency (entry 10).

Table 2.5.1: Scope of the Two-Component Hemiacetal/Oxa-Conjugate Addition Reaction for δ -Hydroxy α,β -Unsaturated Ketones (eq. 8)



Entry ^a	Homoallylic alcohol <i>rac</i> - 11 R		Yield (%) ^b	<i>ds rac</i> - 11/12 ^c
1	Ph(CH ₂) ₂	a	99	≥19:1
2	PhCH ₂	b	97	“
3	Me	c	92	“
4	Br(CH ₂) ₅	d	99	“
5	ⁱ Pr	e	92	“
6	Cy	f	98	“
7	^t Bu	g	95	“
8	(CH ₃) ₂ CHCH ₂	h	96	“
9	(CH ₃) ₂ CH(CH ₂) ₂	i	98	“
10	BnOCH ₂	j	96 ^d	“
11	TIPSOCH ₂	k	96	“
12	TBDPSO(CH ₂) ₂	l	95	“
13	Ph	m	97	“
14	<i>p</i> -MeOPh	n	67 ^e	“
15	<i>p</i> -NO ₂ Ph	o	90	12:1
16	1-Napht	p	99	16:1

^aAll reactions were carried out on 0.5 mmol scale in DCM at room temperature using 10 mol% Bi(NO₃)₃ and 5 equiv. of the aldehyde for 16-160 hours. ^bIsolated yield. ^cDiastereomeric ratio determined by 500 MHz ¹H NMR analysis of crude reaction mixtures. ^d95% on a 50 mmol scale. ^eDiene was a major side product.

2.6 Reaction Optimisation for the δ -Trialkylsilyloxy α,β -Unsaturated Aldehydes

Although the ability to form the *syn*-1,3-dioxanes **12** from the α,β -unsaturated methyl ketones circumvents the necessity to functionalise an ester or amide, the

ability to employ an aldehyde directly would avoid oxidation state adjustments and thereby dramatically improve the synthetic utility of this process.¹² Towards this end, efforts to extend the methodology to the aldehyde substrates were carried out.

Table 2.6.1 outlines the reaction optimisation for the formation of 1,3-*syn*-dioxanes ***rac*-15** from the α,β -unsaturated aldehydes. Initial attempts to apply optimised conditions found for the ketone substrates resulted in the complex mixtures (entry 1).

Table 2.6.1: *Optimisation of the Two-Component Hemiacetal/Oxa-Conjugate Addition Reaction for the δ -Trialkylsilyloxy α,β -Unsaturated Aldehydes*
($R = Ph(CH_2)_2$, eq. 9)

Entry ^a	P	BiX ₃	Yield (%) ^b	Time (h)	<i>ds rac</i> -15/16 ^c
1	H	BiCl ₃	- ^d	18	-
2	“	Bi(NO ₃) ₃	33	“	17:1
3	TES	“	68	92	“
4 ^e	“	“	78	60	≥19:1
5^f	“	“	83	“	“

^aAll reactions were carried out on 0.5 mmol scale in DCM at room temperature using 10 mol% Bi(NO₃)₃ and 5 equiv. of the acetaldehyde. ^bIsolated yield. ^cDiastereomeric ratio determined by 500 MHz ¹H NMR analysis of crude reaction mixtures. ^dComplex mixture. ^e10 equiv. of the acetaldehyde. ^f20 equiv. of the acetaldehyde.

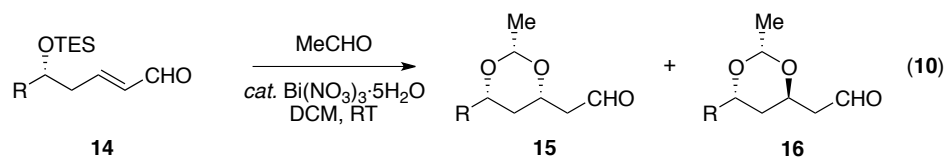
When the bismuth source was changed to a milder Bi(NO₃)₃, the formation of the 1,3-dioxane system became evident by ¹H NMR analysis and the desired product ***rac*-15a** was acquired in 33% isolated yield (entry 2). Unfortunately, the reaction was compromised by the competitive self-condensation of the starting material that led to a reduced yield. Interestingly, treatment of the δ -triethylsilyloxy α,β -unsaturated aldehyde ***rac*-14a** with acetaldehyde in the presence of catalytic Bi(III)

nitrate furnished the 1,3-dioxanes **rac-15a/16a** in 68% yield, favouring the *syn*-diastereoisomer **rac-15a** (entry 3). The marked difference in the efficiency was presumably the result of the triorganosilyl ether controlling the concentration of the secondary alcohol through the rate of protodesilylation.²¹ Finally, the efficiency and selectivity of this process was further improved by increasing the concentration of acetaldehyde and resulted in 83% isolated yield and $\geq 19:1$ selectivity in favour of **rac-15a** (entry 5). It is noteworthy that when other bismuth sources (e. g. BiCl₃, Bi(OTf)₃, BiBr₃) were evaluated in the reaction of **rac-14a** with acetaldehyde, decomposition of the starting material occurred and only complex mixtures were isolated.

2.7 Reaction Substrate Scope for the δ -Trialkylsilyloxy α,β -Unsaturated Aldehydes

With the optimised conditions in hand, the study probed the effect of various substituents on the efficiency and selectivity of the process (Table 2.7.1). Analogously to ketone examples, the diverse TES-protected aldehyde substrates underwent smooth reaction with acetaldehyde to afford the linear and branched products in good yields and with excellent selectivities (*ds* $\geq 19:1$) (entries 1-7). Notably, common alcohol protecting groups (Bn and TBDPS) were stable as well as bromide-containing substrate (entries 4, 8 and 9). The silyl migration was again not an issue and only trace amount of the migration product was observed in the crude reaction mixtures (<5% by ¹H NMR) (entry 9). Although the transformations were less efficient in terms of yield, due to competitive side reactions, uniformly high diastereoselectivities were observed in all cases.

Table 2.7.1: Scope of the Two-Component Hemiacetal/Oxa-Conjugate Addition
Reaction for the δ -Triethylsilyloxy α,β -Unsaturated Aldehydes (eq. 10)



Entry ^a	Homoallylic alcohol <i>rac</i> - 14	Yield (%) ^b	<i>ds rac</i> - 15/16 ^c	
	R			
1	PhCH ₂ CH ₂	a	83	≥19:1
2	PhCH ₂	b	64	“
3	Me	c	56	“
4	Br(CH ₂) ₅	d	74	“
5	ⁱ Pr	e	72	“
6	(CH ₃) ₂ CHCH ₂	f	75	“
7	(CH ₃) ₂ CH(CH ₂) ₂	g	72	“
8	BnOCH ₂	h	72	“
9	TBDPSO(CH ₂) ₂	i	72	“
10	Ph	j	70	“

^aAll reactions were carried out on 0.5 mmol scale in DCM at room temperature using 10 mol% Bi(NO₃)₃ and 20 equiv. of the acetaldehyde for 48-168 hours.

^bIsolated yield. ^cDiastereomeric ratio determined by 500 MHz ¹H NMR analysis of crude reaction mixtures.

2.8 Confirmation of Stereochemistry

In order to prove the stereochemical outcome of the hemiacetal cyclisation, the 1D NOE analysis of 1,3-dioxanes *rac*-**12a** and *rac*-**15a** was carried out. As seen from Figure 2.8.1, strong NOE effect between hydrogens H_A, H_B and H_C suggested that the cyclisation product was the all *syn*-isomer with alkyl substituents residing in the equatorial positions, to effectively minimise the 1,3-diaxial interactions.

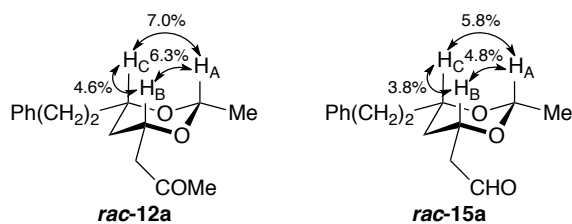


Figure 2.8.1: 1D NOE of the Selected Hemiacetal Cyclisation Products

Further evidence to support the spatial geometry of reaction product was acquired from the X-ray structure of the compound **rac-12p** (Figure 2.8.2). The results obtained correlated with the assignment made on the basis of 1D NOE difference experiments, showing the all *syn* geometry of hydrogen substituents, and confirmed unambiguously the relative configuration of the products from two-component hemiacetal/*oxa*-conjugate addition reaction.

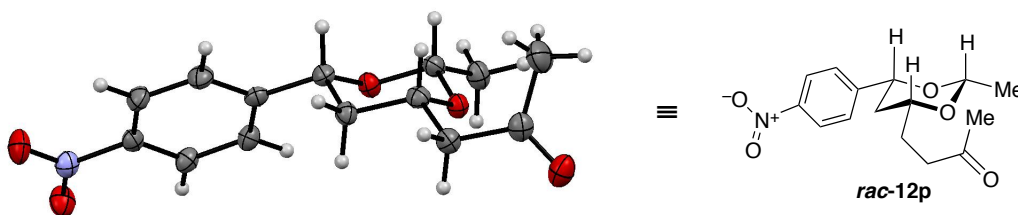
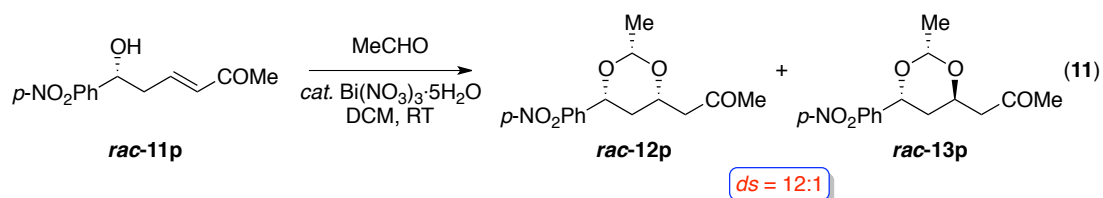


Figure 2.8.2: ORTEP Representation of the X-Ray Structure of **rac-12p**

The less diastereoselective hemiacetal cyclisation reaction of **rac-11p** allowed us to isolate and characterise the minor product **rac-13b** (eq. 11).



Extensive 1D NOE experiments performed on the latter compound showed strong NOE correlations between H_A - H_C protons (6.5%) and H_A - H_5 (5.9%) (Figure 2.8.3). The observed data suggested that the molecule adopted a chair

conformation with two axial hydrogens (A and B), while the H_B residing in the equatorial position.

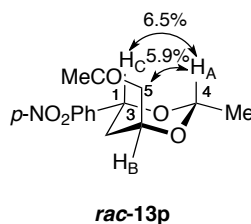
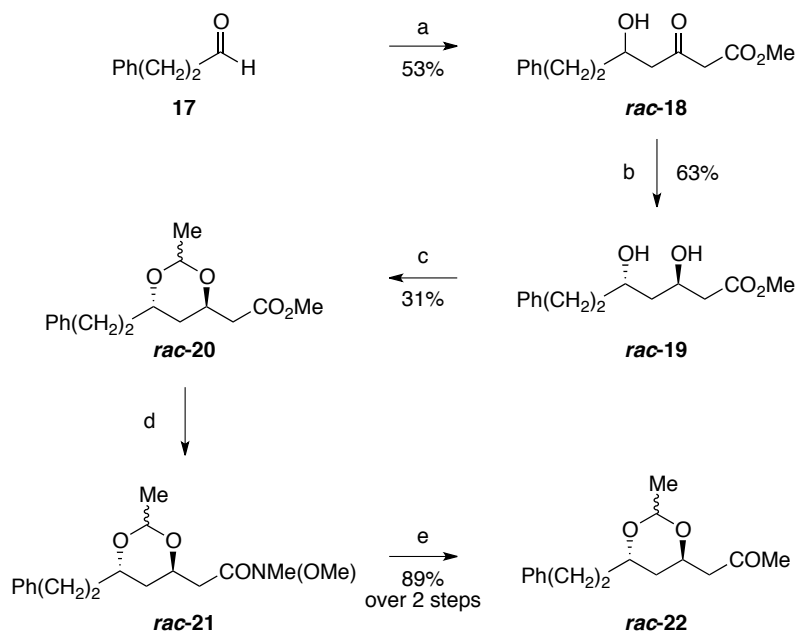


Figure 2.8.3: 1D NOE of the Minor Hemiacetal Cyclisation Product **rac-13b**

Additional studies were carried out to provide more evidence for the stereochemical course of the hemiacetal cyclisation reaction. The protected *anti*-1,3-diol **rac-22** was prepared as outlined in Scheme 2.8.1. Condensation of 3-phenylpropanal with dianion of methyl acetoacetate afforded **rac-18** in 53% yield.

Scheme 2.8.1: Synthesis of the Protected *anti*-1,3-Diol **22**

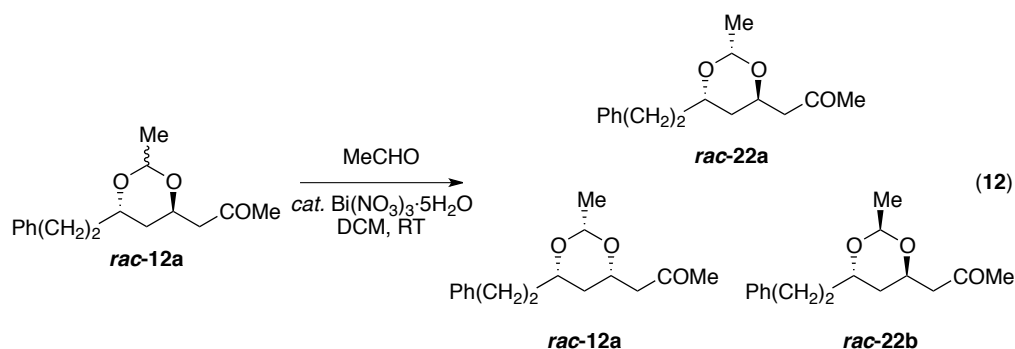


Reaction conditions: a) Methyl acetoacetate, LDA, THF, $-78\text{ }^{\circ}\text{C}$, 53%. b) $n\text{-Bu}_4\text{NBH}(\text{OAc})_3$, MeCN/AcOH (3:1), $-40\text{ }^{\circ}\text{C}$, $ds = 7:1$, 63%. c) Acetaldehyde, *cat.* PPTS, PhH, reflux. d) $\text{MeNH}(\text{OMe})\cdot\text{HCl}$, $i\text{-PrMgCl}$, THF, $0\text{ }^{\circ}\text{C}$. e) MeMgBr , Et_2O , $0\text{ }^{\circ}\text{C}$, 89% over 2 steps.

The 1,3-hydroxyketone **rac-18** reduction using $n\text{-Bu}_4\text{NBH}(\text{OAc})_3$ proceeded with moderate stereocontrol ($ds = 7:1$) to furnish **rac-19** as a mixture of inseparable

diastereoisomers. Protection of diol **rac-19** as an ethylidene acetal using acetaldehyde gave **rac-20** as a mixture of epimers at C4 (acetal ring numbering). Weinreb amide formation, followed by methyl Grignard addition finally afforded ketone **rac-22** as mixture of diastereoisomers at C3 and C4 with a ratio of 7.1:5.1:1 in favour of *anti*-1,3 isomer. The ketone **rac-22** was submitted to the optimised two-component hemiacetal/*oxa*-conjugate addition reaction conditions and the equilibration of diastereoisomers was followed by ^1H NMR. As seen from Table 2.8.1, the relative concentration of the more thermodynamically stable isomer **rac-12a** increased over the time, while the concentration of the less stable isomers **rac-22a** and **rac-22b** decreased. The observed data suggested that the actual cyclisation reaction is reversible and the equilibrium is shifted towards the formation of the thermodynamically more stable product **rac-12a**.

Table 2.8.1: *Equilibration Studies of the anti-1,3-Dioxane 22 (eq. 12)*



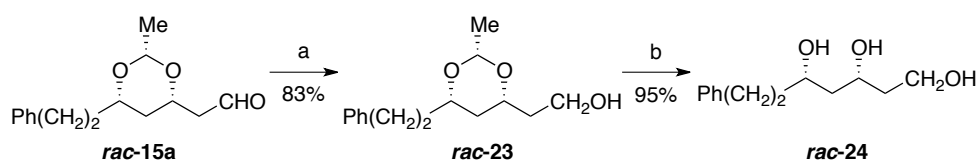
Time	Reaction composition (%) ^a		
	rac-22a	rac-22b	rac-12a
Before reaction	54	38	8
After 18 h	52	35	13
After 42 h	45	35	20

^aDiastereomeric ratio determined by 500 MHz ^1H NMR analysis of crude reaction mixture.

2.9 Deprotection of the 1,3-Ethylidene Acetal

We have shown that δ -trialkylsilyloxy and δ -hydroxy α,β -unsaturated aldehydes and ketones undergo a highly diastereoselective cyclisation with the aliphatic aldehydes to afford the 1,3-*syn* protected diols in high yield. However, in order for the methodology to be synthetically viable, the 1,3-ethylidene acetal group should be easily removed after the cyclisation step. Indeed, sodium borohydride reduction of aldehyde **rac-15a** and subsequent hydrolysis of acetal **rac-23** under mild conditions, using catalytic camphorsulfonic acid, gave triol **rac-24** in excellent overall yield (Scheme 2.9.1). Thus, highlighting the synthetic utility of the developed methodology.

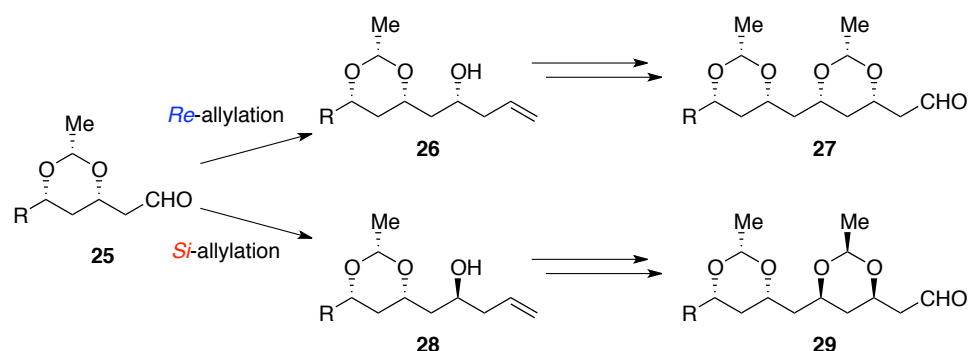
Scheme 2.9.1: Deprotection of the 1,3-Ethylidene Acetal



Reaction conditions: a) NaBH_4 , MeOH, 0 °C, 83%. b) *cat.* CSA, MeOH/ H_2O (10:1), reflux, 95%.

2.10 Synthetic Application of the Developed Methodology. Synthesis of the C18-C28 Fragment of Antibiotic RK-397

We envisioned that our developed methodology could be applied in the iterative process for the synthesis of 1,3,5...-skipped polyol chains (Scheme 2.10.1). Hence, stereoselective allylation of *syn*-1,3-dioxane, followed by successive hemiacetal cyclisation could deliver *syn,syn,syn*-stereotetrad **27**. Furthermore, by changing the facial selectivity of the allylation reaction, *syn,anti,syn*-stereotetrad **29** could be obtained. Moreover, the iteration could be further repeated to produce skipped 1,3-polyol chains of the required configuration.

Scheme 2.10.1: Iterative Synthesis of the 1,3,5-... Skipped Polyols

To prove the concept, we elected to prepare the C4-C12 polyol fragment of antibiotic RK-397 (Figure 2.10.1).²²⁻²⁵

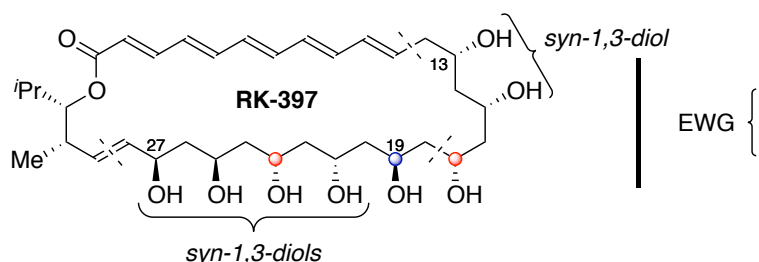
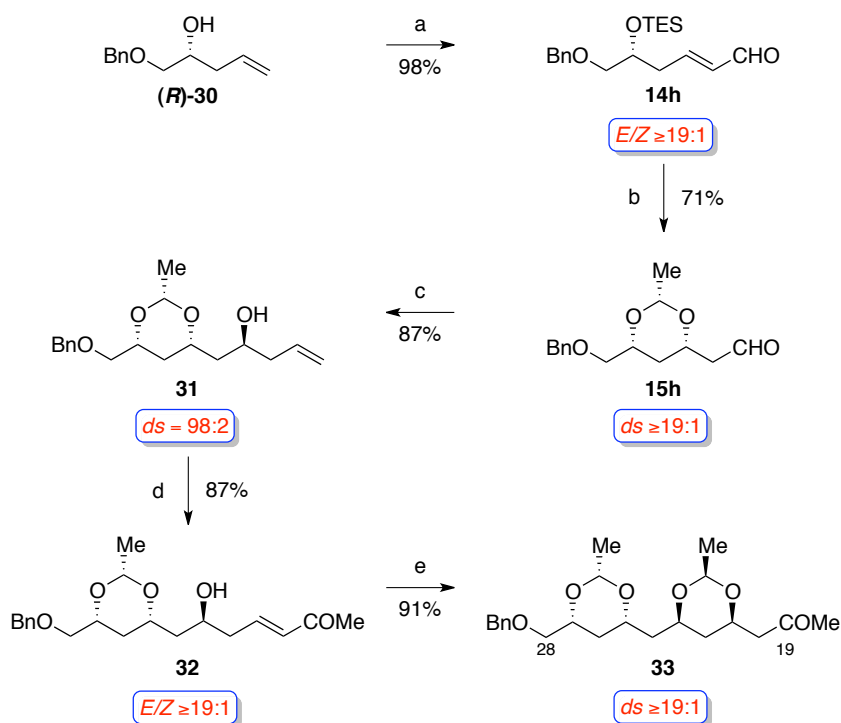


Figure 2.10.1: Mapping of the *syn*-1,3-Dioxanes onto the Polyene Macrolide RK-397 Using the Bismuth-Mediated Two-Component Hemiacetal/Oxa-Conjugate Reaction

The iterative sequence used for fragment synthesis is outlined in the Scheme 2.10.2. The enantioenriched homoallylic alcohol (**R**)-**30** was converted to the δ -triethylsilyloxy α,β -unsaturated aldehyde **14h** in 98% overall yield *via* cross metathesis²⁶ with acrolein mediated by Hoveyda-Grubbs 2nd generation catalyst,²⁷ followed by *in situ* protection of the secondary alcohol at low temperature to suppress the formation of the extended triethylsilyl enol ether. Treatment of **14h** under the optimised reaction conditions for the bismuth-mediated two-component hemiacetal/*oxa*-conjugate addition, furnished the protected *syn*-1,3-dioxane **15h** in 71% yield with excellent diastereocontrol ($ds \geq 19:1$). Stereoselective allylation of

aldehyde **15h** ($ds = 98:2$ by HPLC), using Muruoka's protocol,²⁸ provided the homoallylic alcohol **31** required to demonstrate the iterative process.

Scheme 2.10.2: *Iterative Bismuth-Mediated Two-Component Hemiacetal/Oxa-Conjugate Reaction to the syn-1,3-Dioxanes*



Reaction conditions: a) i. Acrolein, *cat.* HG-II, reflux, DCM. ii. TESOTf, 2,6-lutidine, $-78\text{ }^{\circ}\text{C}$, DCM, $E/Z \geq 19:1$, 98%. b) MeCHO, *cat.* Bi(NO₃)₃, DCM, $ds \geq 19:1$, 71%. c) *cat.* TiCl₄, *cat.* Ti(O^{*i*}Pr)₄, *cat.* BINOL, *cat.* Ag₂O, DCM, $0\text{ }^{\circ}\text{C}$, $ds = 98:2$, 87%. d) Methyl vinyl ketone, *cat.* HG-II, reflux, DCM, $E/Z \geq 19:1$, 87%. e) MeCHO, *cat.* Bi(NO₃)₃, DCM, $ds \geq 19:1$, 91%.

Cross metathesis with methyl vinyl ketone provided the α,β -unsaturated ketone **32** ($E/Z \geq 19:1$), which was treated under analogous conditions outlined for the δ -hydroxy α,β -unsaturated ketones, to afford the *bis*-protected *syn*-1,3-diol **33** in 91% yield and with excellent diastereocontrol ($ds \geq 19:1$ by ¹H-NMR). The advantage of this approach is the operational simplicity coupled with the ability to utilise the α,β -unsaturated aldehydes and ketones, which makes this methodology an extremely attractive approach for preparation of the *syn*-1,3-dioxanes.¹¹ⁱ

2.11 Conclusion

In summary, we have developed a highly diastereoselective bismuth mediated two-component hemiacetal/*oxa*-conjugate addition reaction, which directly provides *syn*-1,3-dioxanes under extremely mild conditions. This operationally simple protocol provides the electron-withdrawing group in the aldehyde and ketone oxidation state, which alleviated the necessity for redox adjustments. The synthetic utility of this approach was highlighted in a five-step synthesis of the C18-C28 fragment of the polyene macrolide antibiotic RK-397 in 48% overall yield. Finally, we envision that this approach will find favour in a number of synthetic applications that require the aldehyde and ketone oxidation states, especially in target-oriented synthesis.^{11,12}

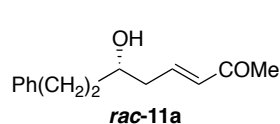
2.12 Experimental Part. General information.

All reactions were carried out under ambient atmosphere with reagent grade solvents, unless otherwise stated. Anhydrous DCM was obtained by passing degassed solvents through activated alumina columns in a Grubbs solvent purification system (*PureSolv MD-6* of *Innovative Technology Inc.*). 2,6-lutidine was distilled from CaH_2 under nitrogen; MgSO_4 or Na_2SO_4 in their anhydrous form were used as drying agents; all other commercially available reagents (*Aldrich*, *Alfa-Aesar*, *Acros*) were purchased and used as received, unless otherwise noted. All compounds were purified by flash chromatography using silica gel 60 (40–63 μm , *FluoroChem*) and gave spectroscopic data consistent with being $\geq 95\%$ the assigned structure. Analytical thin layer chromatography (TLC) was performed on pre-coated 0.25 mm thick silica gel 60-F₂₅₄ plates (*Whatman PE SIL G/UV*); UV light and by treatment with a spray of Pancaldi reagent [$(\text{NH}_4)_6\text{MoO}_4$, $\text{Ce}(\text{SO}_4)_2$, H_2SO_4 , H_2O] followed by heating. The melting points (uncorrected) were obtained from a *Griffin Melting Point Instrument*. Optical rotations ($[\alpha]_{\text{D}}^{20}$) were measured on a *Perkin-Elmer Model 343 plus* polarimeter with a sodium lamp (D line, 589 nm) at ambient temperature (indicated in $^{\circ}\text{C}$ as superscript) using a 1 dm path length quartz cell; solution concentration (c) are given in g/100 mL. HPLC analyses were carried out on an *Agilent 1200 series HPLC* instrument equipped with a diode-array detector using an achiral column *ZORBAX Rx-SIL* (0.46 cm $\varnothing \times$ 25 cm) from *Daicel Chemical Ind.* IR spectra were recorded on a *Perkin-Elmer FT-IR Spectrum 100* spectrometer; wavenumbers (ν) are given in cm^{-1} ; and the abbreviations w (weak, $< 20\%$), m (medium, 20–40%), s (strong, 40–66%), vs (very strong, $> 66\%$) and br (broad) are used to describe the relative intensities of the IR absorbance bands. Mass spectra were obtained through the Chemistry Department Mass Spectrometry

Service, University of Liverpool and EPSRC National Mass Spectrometry Service Centre (Swansea, UK). High resolution chemical ionization (CI) and electrospray ionization (ESI) mass spectra were recorded on a *Fisons Trio-1000* or *LTQ Orbitrap*, and *Micromass LTC* mass spectrometers, respectively. ^1H -NMR and ^{13}C -NMR spectra were recorded on a *Bruker Avance DRX-500* spectrometer in the solvent indicated (CDCl_3 or C_6D_6) at ambient temperature; chemical shifts (δ) are given in ppm and calibrated using the signal of residual undeuterated solvent as internal reference (CDCl_3 : $\delta_{\text{H}} = 7.26$ ppm and $\delta_{\text{C}} = 77.00$ ppm; C_6D_6 : $\delta_{\text{H}} = 7.15$ ppm and $\delta_{\text{C}} = 128.62$ ppm). ^1H -NMR data are reported as follows: chemical shift (multiplicity, 2nd order spin system if available, coupling constant, integration). Coupling constants (J) are reported in Hz and apparent splitting patterns are designated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), app. (apparent) and combinations of these. The reported chemical shifts for broad singlets, and each part of the 2nd order spin systems were averaged. ^{13}C -NMR spectra with complete proton decoupling were described with the aid of an APT sequence, separating methylene and quaternary carbons (e, even), from methyl and methine (o, odd).

2.13 Preparation of the δ -Hydroxy α,β -Unsaturated Ketones

General Procedure: The corresponding homoallylic alcohol (5 mmol) was dissolved in anhydrous DCM (12.5 mL) under an atmosphere of argon and treated with methyl vinyl ketone (2.0 mL, 25 mmol) and Hoveyda-Grubbs 2nd generation catalyst (31.3 mg, 0.05 mmol). The reaction mixture refluxed for *ca.* 2 h (TLC control), then concentrated and purified by flash chromatography to give δ -hydroxy- α,β -unsaturated ketones.



(E)-6-Hydroxy-8-phenyloct-3-en-2-one (*rac*-11a)

Product was obtained after flash chromatography (silica gel, EtOAc/petroleum ether – 1:2) in 84 % yield.

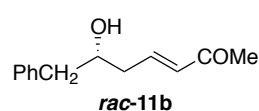
Colour and state: White waxy solid.

¹H NMR (500 MHz, CDCl₃) δ 7.31-7.26 (m, 2H), 7.22-7.19 (m, 3H), 6.83 (dt, *J* = 15.9, 7.4 Hz, 1H), 6.14 (d, *J* = 16.0 Hz, 1H), 3.83-3.77 (m, 1H), 2.81 (app. dt, A of ABM₂, *J*_{AB} = 14.2 Hz, *J*_{AM} = 7.3 Hz, 1H), 2.70 (app. dt, B of ABM₂, *J*_{AB} = 13.9 Hz, *J*_{BM} = 8.0 Hz, 1H), 2.45 (dddd, A of ABMNX, *J*_{AB} = 14.5 Hz, *J*_{AM} = 7.0 Hz, *J*_{AN} = 4.5 Hz, *J*_{AX} = 1.5 Hz, 1H), 2.38 (app. dtd, B of ABM₂X, *J*_{AB} = 14.5 Hz, *J*_{BM} = 7.6 Hz, *J*_{BX} = 1.5 Hz, 1H), 2.25 (s, 3H), 1.86-1.76 (m, 2H), 1.69 (d, *J* = 4.1 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 198.73 (e), 144.46 (o), 141.59 (e), 133.44 (o), 128.52 (o), 128.43 (o), 126.02 (o), 69.85 (o), 40.57 (e), 38.86 (e), 31.97 (e), 27.02 (o).

IR (Neat) 3415 (br), 3026 (w), 2923 (w), 2856 (w), 1666 (s), 1625 (m), 1496 (w), 1455 (w), 1362 (m), 1256 (s), 978 (s) cm⁻¹.

HRMS (CI, [M+NH₄]⁺) calcd for C₁₄H₂₂NO₂ 236.1645, found 236.1647.



(E)-6-Hydroxy-7-phenylhept-3-en-2-one (*rac*-11b)

Product was obtained after flash chromatography (silica gel, EtOAc/hexanes – 1.5:1) in 91% yield.

Colour and state: Colourless oil.

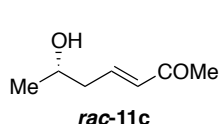
¹H NMR (500 MHz, CDCl₃) δ 7.33-7.30 (m, 2H), 7.26-7.19 (m, 3H), 6.86 (dt, *J* = 15.2, 7.2 Hz, 1H), 6.13 (dd, *J* = 16.0, 0.5 Hz, 1H), 4.01-3.96 (m, 1H), 2.82 (dd, A of ABX, *J*_{AB} = 13.6 Hz, *J*_{AX} = 5.0 Hz, 1H), 2.74 (dd, B of ABX, *J*_{AB} = 13.6 Hz, *J*_{BX} = 8.1 Hz, 1H), 2.50-2.45 (m, 1H), 2.39 (app. dt, B of ABM₂, *J*_{AB} = 14.8 Hz, *J*_{BM} = 7.4 Hz, 1H), 2.24 (s, 3H), 2.04 (br s, 1H).

Chapter 2

^{13}C NMR (125 MHz, CDCl_3) δ 198.76 (e), 144.54 (o), 137.72 (e), 133.45 (o), 129.43 (o), 128.73 (o), 126.79 (o), 71.42 (o), 43.85 (e), 39.62 (e), 26.95 (o).

IR (Neat) 3411 (br), 3028 (w), 2920 (w), 1665 (s), 1625 (m), 1496 (w), 1454 (w), 1361 (m), 1256 (s), 976 (s) cm^{-1} .

HRMS (CI, $[\text{M}+\text{H}]^+$) calcd for $\text{C}_{13}\text{H}_{17}\text{O}_2$ 205.1223, found 205.1225.



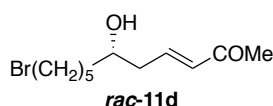
(E)-6-Hydroxyhept-3-en-2-one (*rac*-11c)²⁹

Product was obtained after flash chromatography (silica gel, EtOAc/hexanes – 2:1) in 49% yield.

Colour and state: Colourless volatile oil.

^1H NMR (500 MHz, CDCl_3) δ 6.83 (dt, J = 16.0, 7.3 Hz, 1H), 6.14 (dt, J = 16.0, 1.3 Hz, 1H), 3.99-3.97 (m, 1H), 2.43-2.35 (m, 2H), 2.26 (s, 3H), 1.71 (br s, 1H), 1.25 (d, J = 6.2 Hz, 3H).

IR (Neat) 3410 (br), 2969 (w), 2930 (w), 1665 (s), 1626 (m), 1362 (m), 1255 (s), 980 (s) cm^{-1} .



(E)-11-Bromo-6-hydroxyundec-3-en-2-one (*rac*-11d)

Product was obtained after flash chromatography (silica gel, EtOAc/hexanes – 1:1.5) in 95% yield.

Colour and state: Colourless oil.

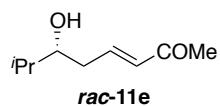
^1H NMR (500 MHz, CDCl_3) δ 6.83 (dt, J = 15.5, 7.6 Hz, 1H), 6.13 (dd, J = 16.0, 0.8 Hz, 1H), 3.79-3.75 (m, 1H), 3.40 (td, J = 6.7, 0.5 Hz, 2H), 2.45-2.40 (m, 1H), 2.38-2.29 (m, 1H), 2.25 (d, J = 0.7 Hz, 3H), 1.88-1.83 (m, 3H), 1.51-1.34 (m, 6H).

^{13}C NMR (125 MHz, CDCl_3) δ 198.62 (e), 144.39 (o), 133.46 (o), 70.42 (o), 40.48 (e), 37.05 (e), 33.84 (e), 32.62 (e), 28.03 (e), 27.05 (o), 24.78 (e).

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IR (Neat) 3421 (br), 2934 (m), 2859 (w), 1668 (s), 1625 (m), 1361 (m), 1255 (s), 978 (s) cm^{-1} .

HRMS (CI, $[\text{M}+\text{NH}_4]^+$) calcd for $\text{C}_{11}\text{H}_{23}^{79}\text{BrNO}_2$ 280.0912, found 280.0907.



(E)-6-Hydroxy-7-methyloct-3-en-2-one (*rac*-11e)

Product was obtained after flash chromatography (silica gel, EtOAc/hexanes – 1:2) in 74% yield.

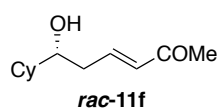
Colour and state: Colourless oil.

^1H NMR (500 MHz, CDCl_3) δ 6.86 (dt, $J = 15.9, 7.3$ Hz, 1H), 6.13 (dt, $J = 16.0, 1.3$ Hz, 1H), 3.54-3.48 (m, 1H), 2.41 (dddd, $J = 14.7, 6.9, 3.7, 1.5$ Hz, 1H), 2.36-2.28 (m, 1H), 2.24 (s, 3H), 1.91 (br s, 1H), 1.68 (septet-d, $J = 6.8, 5.8$ Hz, 1H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 198.71 (e), 145.45 (o), 133.18 (o), 75.45 (o), 37.37 (e), 33.59 (o), 26.90 (o), 18.65 (o), 17.34 (o).

IR (Neat) 3435 (br), 2960 (w), 2875 (w), 1663 (s), 1625 (m), 1362 (m), 1256 (s), 978 (s) cm^{-1} .

HRMS (CI, $[\text{M}+\text{NH}_4]^+$) calcd for $\text{C}_9\text{H}_{20}\text{NO}_2$ 174.1489, found 174.1490.



(E)-6-Cyclohexyl-6-hydroxyhex-3-en-2-one (*rac*-11f)

Product was obtained after flash chromatography (silica gel, Et₂O/hexanes – 1:1) in 85% yield as clear oil.

Colour and state: Colourless oil.

^1H NMR (500 MHz, CDCl_3) δ 6.87 (dt, $J = 15.9, 7.3$ Hz, 1H), 6.15 (dt, $J = 16.0, 1.3$ Hz, 1H), 3.54-3.50 (m, 1H), 2.45 (dddd, $J = 14.6, 6.9, 3.6, 1.5$ Hz, 1H), 2.38-2.30 (m,

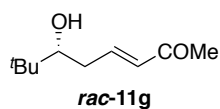
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1H), 2.26 (s, 3H), 1.85-1.74 (m, 3H), 1.69-1.66 (m, 2H), 1.59 (br s, 1H), 1.40-1.32 (m, 1H), 1.29-0.97 (m, 5H).

¹³C NMR (125 MHz, CDCl₃) δ 198.56 (e), 144.31 (o), 133.30 (o), 74.92 (o), 43.49 (o), 37.36 (e), 29.06 (e), 27.90 (e), 26.95 (o), 26.37 (e), 26.15 (e), 26.00 (e).

IR (Neat) 3420 (br), 2923 (s), 2852 (m), 1667 (s), 1625 (m), 1362 (m), 1256 (s), 976 (s).

HRMS (CI, [M+H]⁺) calcd for C₁₂H₂₁O₂ 197.1536, found 197.1533.



(E)-6-Hydroxy-7,7-dimethyloct-3-en-2-one (rac-11g)

Product was obtained after flash chromatography (silica gel, Et₂O/hexanes – 1:1) in 86% yield.

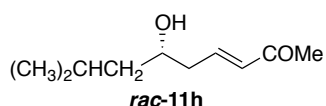
Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 6.90 (dt, *J* = 16.0, 7.2 Hz, 1H), 6.14 (dt, *J* = 16.0, 1.4 Hz, 1H), 3.38 (ddd, *J* = 10.4, 4.9, 2.2 Hz, 1H), 2.46 (app. ddt, *J* = 14.7, 6.7, 1.8 Hz, 1H), 2.25 (s, 3H), 2.21 (dddd, *J* = 14.7, 10.4, 7.5, 1.3 Hz, 1H), 1.68 (d, *J* = 4.9 Hz, 1H), 0.93 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 198.60 (e), 146.57 (o), 132.99 (o), 78.57 (o), 35.09 (e), 35.04 (e), 26.86 (o), 25.58 (o).

IR (Neat) 3429 (br), 2960 (m), 2875 (m), 1665 (s), 1625 (m), 1041 (m) cm⁻¹.

HRMS (CI, [M+H]⁺) calcd for C₁₀H₂₀O₂ 171.1385, found 171.1387.



(E)-6-Hydroxy-8-methylnon-3-en-2-one (rac-11h)

Product was obtained after flash chromatography (silica gel, EtOAc/hexanes – 1:3) in 84% yield.

Colour and state: Colourless oil.

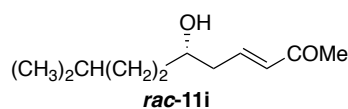
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^1H NMR (500 MHz, CDCl_3) δ 6.85 (dt, $J = 15.9, 7.3$ Hz, 1H), 6.14 (dt, $J = 16.0, 1.3$ Hz, 1H), 3.89-3.83 (m, 1H), 2.42 (dddd, A of ABMNX, $J_{AB} = 14.5$ Hz, $J_{AM} = 7.0$, $J_{AN} = 4.3$, $J_{AX} = 1.5$ Hz, 1H), 2.32 (dtd, B of ABM₂X, $J_{AB} = 14.7$ Hz, $J_{BM} = 7.4$, $J_{BX} = 1.2$ Hz, 1H), 2.26 (s, 3H), 1.82-1.73 (m, 1H), 1.63 (d, $J = 4.9$ Hz, 1H), 1.44 (ddd, A of ABXY, $J_{AB} = 14.0$ Hz, $J_{AX} = 8.9$ Hz, $J_{AY} = 5.3$ Hz, 1H), 1.26 (ddd, B of ABXY, $J_{AB} = 13.7$ Hz, $J_{BX} = 9.0$ Hz, $J_{BY} = 4.4$ Hz, 1H), 0.93 (d, $J = 6.7$ Hz, 3H), 0.91 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 199.10 (e), 145.50 (o), 133.09 (o), 68.35 (o), 46.35 (e), 40.98 (e), 26.74 (o), 24.44 (o), 23.29 (o), 21.92 (o).

IR (Neat) 3422 (br), 2955 (m), 2928 (w), 2870 (w), 1667 (s), 1626 (m), 1364 (m), 1256 (m), 974 (m) cm^{-1} .

HRMS (CI, $[\text{M}+\text{NH}_4]^+$) calcd for $\text{C}_{10}\text{H}_{22}\text{NO}_2$ 188.1645, found 188.1640.



(E)-6-Hydroxy-9-methyldec-3-en-2-one (rac-11i)

Product was obtained after flash chromatography (silica gel, EtOAc/hexanes – 1:1.5) in 70% yield.

Colour and state: Colourless oil.

^1H NMR (500 MHz, CDCl_3) δ 6.84 (dt, $J = 15.9, 7.3$ Hz, 1H), 6.12 (dt, $J = 16.0, 1.3$ Hz, 1H), 3.77-3.70 (m, 1H), 2.42 (dddd, A of ABMNX, $J_{AB} = 14.5$ Hz, $J_{AM} = 7.0$ Hz, $J_{AN} = 4.3$ Hz, $J_{AX} = 1.5$ Hz, 1H), 2.36-2.29 (m, 1H), 2.24 (s, 3H), 1.91 (br s, 1H), 1.57-1.42 (m, 3H), 1.35-1.27 (m, 1H), 1.23-1.15 (m, 1H), 0.88 (d, $J = 6.6$ Hz, 3H), 0.87 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 198.57 (e), 144.57 (o), 133.41 (o), 70.97 (o), 40.37 (e), 35.17 (e), 34.69 (e), 28.03 (o), 26.97 (o), 22.63 (o), 22.50 (o).

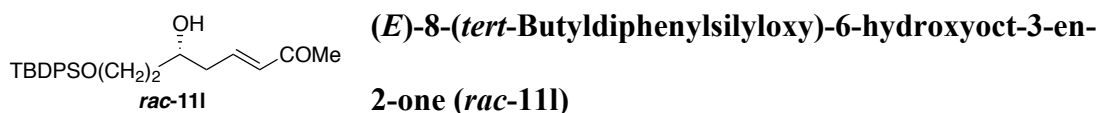
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(dd, B of ABX, $J_{AB} = 9.8$ Hz, $J_{BX} = 6.8$ Hz, 1H), 2.62 (d, $J = 4.1$ Hz, 1H), 2.41-2.38 (m, 2H), 2.25 (s, 3H), 1.18-1.04 (m, 21H).

^{13}C NMR (125 MHz, CDCl_3) δ 198.44 (e), 144.07 (o), 133.33 (o), 70.73 (o), 66.90 (e), 36.20 (e), 26.85 (o), 17.94 (o), 11.88 (o).

IR (Neat) 3435 (br), 2942 (m), 2866 (m), 1672 (m), 1627 (w), 1463 (w), 1362 (w), 1254 (m), 1123 (m), 882 (m) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{16}\text{H}_{32}\text{O}_3\text{NaSi}$ 323.2018, found 323.2007.



Product was obtained after flash chromatography (silica gel, Et_2O /petroleum ether – 1:1.2, 1:1) in 95% yield.

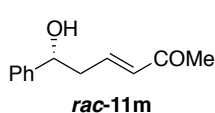
Colour and state: Colourless oil.

^1H NMR (500 MHz, CDCl_3) δ 7.68 (d, $J = 7.0$ Hz, 4H), 7.45-7.38 (m, 6H), 6.89 (dt, $J = 15.9, 7.3$ Hz, 1H), 6.13 (d, $J = 16.0$ Hz, 1H), 4.12-4.06 (m, 1H), 3.89 (dt, A of ABM_2 , $J_{AB} = 10.4$ Hz, $J_{AM} = 5.0$ Hz, 1H), 3.86 (dt, B of ABM_2 , $J_{AB} = 10.5$ Hz, $J_{BM} = 4.1$ Hz, 1H), 3.70 (s, 1H), 2.47-2.38 (m, 2H), 2.25 (s, 3H), 1.78 (dtd, $J = 14.0, 8.9, 5.0$ Hz, 1H), 1.69-1.64 (m, 1H), 1.06 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ 198.74 (e), 144.82 (o), 135.56 (o), 135.54 (o), 133.34 (o), 132.81 (e), 132.73 (e), 130.00 (o), 129.98 (o), 127.90 (o), 70.57 (o), 63.26 (e), 40.53 (e), 38.10 (e), 26.85 (o), 19.06 (e).

IR (Neat) 3439 (br), 3071 (w), 3048 (w), 2931 (m), 2857 (m), 1671 (m), 1626 (w), 1589 (w), 1427 (m), 1106 (s), 980 (m), 702 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{24}\text{H}_{32}\text{O}_3\text{NaSi}$ 419.2018, found 419.2029.



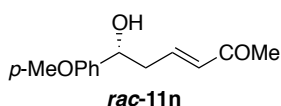
(E)-6-Hydroxy-6-phenylhex-3-en-2-one (*rac*-11m)³⁰

Product was obtained after flash chromatography (silica gel, EtOAc/hexanes – 1.5:1) in 79% yield.

Colour and state: Yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 7.38-7.28 (m, 5H), 6.81 (dt, *J* = 16.0, 7.3 Hz, 1H), 6.12 (d, *J* = 16.0 Hz, 1H), 4.85 (ddd, *J* = 7.6, 4.8, 2.8, Hz, 1H), 2.69 (dt, *J* = 15.1, 7.9 Hz, 1H), 2.66-2.61 (m, 1H), 2.28 (br s, 1H), 2.23 (s, 3H).

IR (Neat) 3405 (br), 3030 (w), 2919 (w), 1666 (s), 1624 (m), 1494 (w), 1453 (w), 1362 (m), 1257 (m), 1048 (m), 976 (m) cm⁻¹.



(E)-6-Hydroxy-6-(4-methoxyphenyl)hex-3-en-2-one

(*rac*-11o)

Product was obtained after flash chromatography (silica gel, EtOAc/hexanes – 1:1.5) in 86% yield.

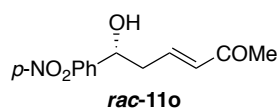
Colour and state: Yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 7.29-7.26 (m, 2H), 6.90-6.88 (m, 2H), 6.79 (dt, *J* = 16.0, 7.2 Hz, 1H), 6.12 (dt, *J* = 16.0, 1.4 Hz, 1H), 4.79 (dd, *J* = 7.6, 5.3 Hz, 1H), 3.81 (s, 3H), 2.72-2.58 (m, 2H), 2.22 (s, 3H), 2.07 (br s, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 198.55 (e), 159.36 (e), 143.97 (o), 135.56 (e), 133.50 (o), 126.99 (o), 114.03 (o), 72.87 (o), 55.33 (o), 41.99 (e), 26.91 (o).

IR (Neat) 3413 (br), 2911 (w), 1665 (m), 1611 (m), 1512 (m), 1361 (w), 1245 (s), 1174 (m) cm⁻¹.

HRMS (CI, [M+NH₄]⁺) calcd for C₁₃H₂₀O₃N 238.1438, found 238.1436.



(E)-6-Hydroxy-6-(4-nitrophenyl)hex-3-en-2-one (*rac*-11o)

Product was obtained after flash chromatography (silica gel, EtOAc/hexanes – 1.2:1) in 95% yield.

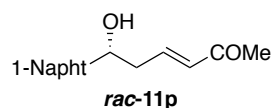
Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 8.23-8.20 (m, 2H), 7.54 (s, *J* = 8.7 Hz, 2H), 6.79 (dt, *J* = 15.9, 7.3 Hz, 1H), 6.14 (d, *J* = 16.0 Hz, 1H), 5.00 (app. t, *J* = 6.3 Hz, 1H), 2.67-2.64 (m, 2H), 2.56 (br s, 1H), 2.23 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 198.27 (e), 150.62 (o), 142.28 (o), 134.00 (o), 126.50 (o), 123.89 (o), 72.11 (o), 42.02 (e), 27.23 (o).

IR (Neat) 3410 (br), 2922 (w), 2866 (m), 1710 (m), 1668 (m), 1626 (m), 1600 (m), 1518 (s), 1345 (s), 1258 (m), 856 (m) cm⁻¹.

HRMS (CI, [NH₄]⁺) calcd for C₁₂H₁₇O₄N₂ 253.1183, found 253.1183.



(E)-6-Hydroxy-6-(naphthalen-1-yl)hex-3-en-2-one

(*rac*-11p)

Product was obtained after flash chromatography (silica gel, Et₂O/hexanes – 1:1.5) in 92% yield.

Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 8.04 (d, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 7.1 Hz, 1H), 7.56-7.48 (m, 3H), 6.92 (dt, *J* = 16.0, 7.3 Hz, 1H), 6.17 (d, *J* = 16.0 Hz, 1H), 5.64 (app. dt, *J* = 7.9, 3.9 Hz, 1H), 2.89-2.77 (m, 2H), 2.23-2.22 (m, 4H).

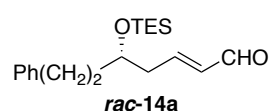
¹³C NMR (125 MHz, CDCl₃) δ 198.60 (e), 144.20 (o), 138.98 (e), 133.84 (e), 133.51 (o), 130.03 (e), 129.13 (o), 128.47 (o), 126.36 (o), 125.77 (o), 125.47 (o), 122.82 (o), 122.65 (o), 69.94 (o), 41.13 (e), 26.88 (o).

IR (Neat) 3514 (br), 2908 (w), 1655 (s), 1638 (s), 1362 (m), 1257 (s), 973 (s), 782 (s) cm^{-1} .

HRMS (CI, $[\text{M}+\text{NH}_4]^+$) calcd for $\text{C}_{16}\text{H}_{20}\text{O}_2\text{N}$ 258.1494 found 258.1497.

2.14 Preparation of the δ -Triethylsilyloxy α,β -Unsaturated Aldehydes

General Procedure: The corresponding homoallylic alcohol (5 mmol) was dissolved in anhydrous DCM (12.5 mL) under an atmosphere of argon and treated with acrolein (25 mmol) and Hoveyda-Grubbs 2nd generation catalyst (47.0 mg, 0.075 mmol). The reaction mixture was refluxed for *ca.* 4 h (TLC control), then concentrated *in vacuo* and redissolved in anhydrous DCM (12.5 mL) under an atmosphere of argon. The solution was cooled to -78°C and treated sequentially with 2,6-lutidine (1.45 mL, 12.5 mmol) and TESOTf (2.26 mL, 10 mmol). The reaction mixture was stirred at that temperature until consumption of the starting material (TLC control), before it was quenched with saturated aqueous NaHCO_3 , warmed to room temperature and partitioned between water and diethyl ether. Phases were separated and the aqueous layer was washed with Et_2O (2x). The combined organic phases were successively washed with saturated aqueous NH_4Cl , water, brine, dried (MgSO_4), filtered and concentrated *in vacuo* to afford a crude product, which was purified by flash chromatography (silica gel) to give δ -triethylsilyloxy α,β -unsaturated aldehydes.



(*E*)-7-Phenyl-5-(triethylsilyloxy)hept-2-enal (*rac*-14a)

The product was obtained after flash chromatography (silica gel, Et_2O /hexanes – 1:9) in 71% yield.

Colour and state: Colourless oil.

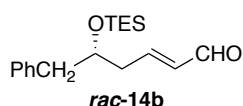
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¹H NMR (500 MHz, CDCl₃) δ 9.52 (d, *J* = 7.9 Hz, 1H), 7.30-7.26 (m, 2H), 7.22-7.16 (m, 3H), 6.90 (dt, *J* = 15.2, 7.6 Hz, 1H), 6.16 (dd, *J* = 15.6, 7.9 Hz, 1H), 3.92 (quintet, *J* = 5.7 Hz, 1H), 2.74-2.50 (m, 4H), 1.86-1.75 (m, 2H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.62 (q, *J* = 8.0 Hz, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 193.89 (o), 154.94 (o), 141.80 (e), 134.93 (o), 128.48 (o), 128.29 (o), 125.96 (o), 70.61 (o), 40.52 (e), 39.14 (e), 31.77 (e), 6.95 (o), 5.04 (e).

IR (Neat) 2953 (w), 2912 (w), 2876 (w), 1692 (s), 1638 (w), 1496 (w), 1456 (w), 1239 (w), 1061 (m), 1004 (m), 976 (m), 725 (vs), 699 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₁₉H₃₀O₂NaSi 341.1913, found 341.1899.



(*E*)-6-Phenyl-5-(triethylsilyloxy)hex-2-enal (*rac*-14b)

The product was obtained after flash chromatography (silica gel, Et₂O/petroleum ether – 0%, 2%, 4%, 8%) in 86% yield.

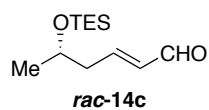
Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 9.51 (d, *J* = 8.0 Hz, 1H), 7.31-7.27 (m, 2H), 7.24-7.19 (m, 1H), 7.17-7.14 (m, 2H), 6.90 (ddd, *J* = 15.5, 7.8, 7.0 Hz, 1H), 6.12 (ddt, *J* = 15.7, 7.9, 1.2 Hz, 1H), 4.07 (quintet, *J* = 6.0 Hz, 1H), 2.82 (dd, A of ABX, *J*_{AB} = 13.4 Hz, *J*_{AX} = 6.2 Hz, 1H), 2.71 (dd, B of ABX, *J*_{AB} = 13.4 Hz, *J*_{BX} = 7.0 Hz, 1H), 2.50-2.40 (m, 2H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.55 (dq, A of ABM₃, *J*_{AB} = 15.5 Hz, *J*_{AM} = 7.6 Hz, 3H), 0.51 (dq, B of ABM₃, *J*_{AB} = 15.2 Hz, *J*_{BM} = 8.2 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 193.84 (o), 155.10 (o), 138.11 (e), 135.03 (o), 129.57 (o), 128.42 (o), 126.52 (o), 72.39 (o), 44.17 (e), 39.96 (e), 6.89 (o), 4.84 (e).

IR (Neat) 2953 (m), 2912 (w), 2876 (m), 2810 (w), 1691 (s), 1636 (w), 1496 (w), 1455 (w), 1083 (m), 1005 (m), 977 (m), 740 (vs), 700 (s) cm⁻¹.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{18}H_{28}O_2NaSi$ 327.1756, found 327.1755.



(E)-5-(Triethylsilyloxy)hex-2-enal (*rac*-14c)

The product was obtained after flash chromatography (silica gel, Et_2O /petroleum ether – 0%, 2%, 4%, 8%) in 85% yield.

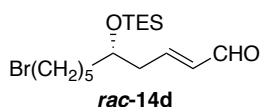
Colour and state: Colourless oil.

1H NMR (500 MHz, $CDCl_3$) δ 9.50 (d, $J = 7.9$ Hz, 1H), 6.88 (dt, $J = 15.4, 7.6$ Hz, 1H), 6.13 (dd, $J = 15.7, 7.9$ Hz, 1H), 4.00 (sextet, $J = 6.0$ Hz, 1H), 2.45 (m, 2H), 1.18 (d, $J = 6.1$ Hz, 3H), 0.94 (t, $J = 8.0$ Hz, 9H), 0.64-0.52 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 193.98 (o), 155.39 (o), 134.72 (o), 67.17 (o), 42.79 (e), 23.86 (o), 6.83 (o), 4.85 (e).

IR (Neat) 2955 (m), 2911 (w), 2877 (m), 2805 (w), 1694 (s), 1639 (w), 1126 (m), 1005 (m), 745 (vs) cm^{-1} .

HRMS (ESI, $[M+Na]^+$) calcd for $C_{12}H_{24}O_2NaSi$ 251.1443, found 251.1454.



(E)-10-Bromo-5-(triethylsilyloxy)dec-2-enal (*rac*-14d)

The product was obtained after flash chromatography (silica gel, Et_2O /petroleum ether – 0% to 8%) in 89% yield.

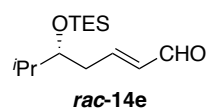
Colour and state: Colourless oil.

1H NMR (500 MHz, $CDCl_3$) δ 9.50 (d, $J = 7.9$ Hz, 1H), 6.87 (dt, $J = 15.3, 7.6$ Hz, 1H), 6.12 (dd, $J = 15.7, 7.9$ Hz, 1H), 3.84 (quintet, $J = 5.7$ Hz, 1H), 3.38 (t, $J = 6.8$ Hz, 2H), 2.52-2.41 (m, 2H), 1.84 (quintet, $J = 7.0$ Hz, 2H), 1.50-1.26 (m, 6H), 0.94 (t, $J = 8.0$ Hz, 9H), 0.58 (q, $J = 8.0$ Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 193.84 (o), 155.10 (o), 134.84 (o), 70.82 (o), 40.52 (e), 37.12 (e), 33.74 (e), 32.67 (e), 28.18 (e), 24.51 (e), 6.90 (o), 4.99 (e).

IR (Neat) 2937 (m), 2876 (m), 2810 (w), 2731 (w), 1692 (s), 1638 (w), 1074 (m), 1005 (m), 725 (vs) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{16}\text{H}_{31}\text{O}_2\text{NaSi}^{79}\text{Br}$ 385.1174 found 385.1165.



(E)-6-Methyl-5-(triethylsilyloxy)hept-2-enal (*rac*-14e)

The product was obtained after flash chromatography (silica gel, Et_2O /petroleum ether – 1:15) in 79% yield.

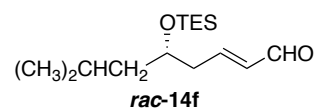
Colour and state: Colourless oil.

^1H NMR (500 MHz, CDCl_3) δ 9.44 (d, $J = 7.9$ Hz, 1H), 6.83 (dt, $J = 15.3, 7.4$ Hz, 1H), 6.07 (ddt, $J = 15.6, 7.9, 1.3$ Hz, 1H), 3.57 (q, $J = 5.5$ Hz, 1H), 2.44-2.34 (m, 2H), 1.68-1.59 (m, 1H), 0.88 (t, $J = 8.0$ Hz, 9H), 0.82 (d, $J = 6.8$ Hz, 3H), 0.81 (d, $J = 6.8$ Hz, 3H), 0.53 (q, $J = 8.0$ Hz, 6H).

^{13}C NMR (125 MHz, CDCl_3) δ 193.62 (o), 155.90 (o), 134.51 (o), 75.84 (o), 37.07 (e), 33.50 (o), 17.94 (o), 17.70 (o), 6.84 (o), 5.01 (e).

IR (Neat) 2957 (m), 2912 (w), 2877 (m), 2805 (w), 2731 (w), 1692 (s), 1638 (w), 1460 (w), 1239 (w), 1061 (s), 1006 (m), 724 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{14}\text{H}_{28}\text{O}_2\text{NaSi}$ 279.1756, found 279.1746.



(E)-7-Methyl-5-(triethylsilyloxy)oct-2-enal (*rac*-14f)

The product was obtained after flash chromatography (silica gel, Et_2O /petroleum ether – 1:15, 1:13) in 74% yield.

Colour and state: Colourless oil.

^1H NMR (500 MHz, CDCl_3) δ 9.45 (d, $J = 7.9$ Hz, 1H), 6.84 (ddd, $J = 15.7, 7.7, 7.2$ Hz, 1H), 6.07 (ddt, $J = 15.7, 7.9, 1.2$ Hz, 1H), 3.87 (app. dq, $J = 12.5, 5.7$ Hz, 1H), 2.47 (dddd, A of ABMNX, $J_{AB} = 14.5$ Hz, $J_{AM} = 6.8$ Hz, $J_{AN} = 5.3$ Hz, $J_{AX} = 1.5$ Hz,

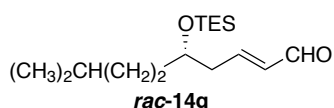
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1H), 2.37 (dddd, B of ABMN_X, $J_{AB} = 14.5$ Hz, $J_{BM} = 6.6$ Hz, $J_{BN} = 5.4$ Hz, $J_{BX} = 1.2$ Hz, 1H) 1.60 (nonet, $J = 6.7$ Hz, 1H), 1.33 (app. dt, A of ABX₂, $J_{AB} = 13.7$ Hz, $J_{AX} = 6.9$ Hz, 1H), 1.20 (ddd, B of ABXY, $J_{AB} = 13.5$ Hz, $J_{BX} = 7.2$ Hz, $J_{BY} = 6.2$ Hz, 1H), 0.89 (t, $J = 8.0$ Hz, 9H), 0.83 (d, $J = 6.7$ Hz, 3H), 0.82 (d, $J = 6.7$ Hz, 3H), 0.54 (q, $J = 8.0$ Hz, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 193.69 (o), 155.10 (o), 134.81 (o), 69.13 (o), 46.56 (e), 40.64 (e), 24.39 (o), 22.83 (o), 22.63 (o), 6.81 (o), 4.97 (e).

IR (Neat) 2955 (m), 2913 (m), 2877 (m), 2805 (w), 2729 (w), 1694 (s), 1637 (w), 1238 (w), 1065 (s), 1005 (m), 976 (m), 738 (s), 725 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₁₅H₃₀O₂NaSi 293.1913, found 293.1913.



(E)-8-Methyl-5-(triethylsilyloxy)non-2-enal (*rac*-14g)

The product was obtained after flash chromatography (silica gel, Et₂O/petroleum ether – 0% to 5%) in 85% yield.

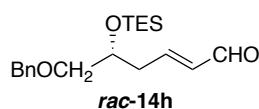
Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 9.48 (d, $J = 8.0$ Hz, 1H), 6.87 (dt, $J = 15.3, 7.5$ Hz, 1H), 6.11 (dd, $J = 15.7, 8.0$ Hz, 1H), 3.79 (quintet, $J = 5.8$ Hz, 1H), 2.52-2.39 (m, 2H), 1.51-1.37 (m, 3H), 1.23-1.08 (m, 2H), 0.92 (t, $J = 8.0$ Hz, 9H), 0.84 (d, $J = 6.6$ Hz, 6H), 0.56 (q, $J = 8.0$ Hz, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 193.88 (o), 155.46 (o), 134.74 (o), 71.29 (o), 40.41 (e), 35.16 (e), 34.40 (e), 28.08 (o), 22.58 (o), 22.52 (o), 6.86 (o), 4.95 (e).

IR (Neat) 2954 (m), 2912 (m), 2876 (m), 2807 (w), 2729 (w), 1695 (s), 1638 (w), 1069 (m), 1005 (m), 977 (m), 725 (vs) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₁₆H₃₂O₂NaSi 307.2069, found 307.2076.



(E)-6-(Benzyloxy)-5-(triethylsilyloxy)hex-2-enal (*rac*-14h)

The product was obtained after flash chromatography (silica gel, Et₂O/petroleum ether – 0% to 8%) in 90% yield.

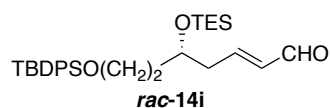
Colour and state: Yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 9.48 (d, *J* = 8.0 Hz, 1H), 7.37-7.28 (m, 5H), 6.87 (dt, *J* = 15.3, 7.6 Hz, 1H), 6.15 (ddt, *J* = 15.6, 7.9, 1.2 Hz, 1H), 4.53 (d, A of AB, *J*_{AB} = 12.0 Hz, 1H), 4.50 (d, B of AB, *J*_{AB} = 12.0 Hz, 1H), 4.02-3.98 (m, 1H), 3.44 (dd, A of ABX, *J*_{AB} = 9.4 Hz, *J*_{AX} = 5.0 Hz, 1H), 3.34 (dd, B of ABX, *J*_{AB} = 9.4 Hz, *J*_{BX} = 6.6 Hz, 1H), 2.62 (dddd, A of ABMXY, *J*_{AB} = 14.4 Hz, *J*_{AM} = 6.7 Hz, *J*_{AX} = 5.0 Hz, *J*_{AY} = 1.6 Hz, 1H), 2.54 (dddd, B of ABMXY, *J*_{AB} = 14.3 Hz, *J*_{BM} = 7.7 Hz, *J*_{BX} = 6.5 Hz, *J*_{BY} = 1.1 Hz, 1H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.65-0.52 (m, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 193.98 (o), 155.03 (o), 137.94 (e), 134.97 (o), 128.43 (o), 127.79 (o), 127.76 (o), 73.69 (e), 73.43 (e), 69.96 (o), 38.20 (e), 6.83 (o), 4.85 (e).

IR (Neat) 2954 (w), 2906 (w), 2876 (w), 2805 (w), 2729 (w), 1691 (s), 1638 (w), 1497 (w), 1087 (m), 977 (m), 733 (vs), 698 (m) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₁₉H₃₀O₃NaSi 357.1862, found 357.1872.



(E)-7-(*tert*-Butyldiphenylsilyloxy)-5-

(triethylsilyloxy)hept-2-enal (*rac*-14i)

The product was obtained after flash chromatography (silica gel, Et₂O/petroleum ether – 0% to 6%) with 79% yield.

Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 9.50 (d, *J* = 7.9 Hz, 1H), 7.66-7.63 (m, 4H), 7.45-7.36 (m, 6H), 6.68 (dt, *J* = 15.3, 7.6 Hz, 1H), 6.10 (dd, *J* = 15.7, 8.0 Hz, 1H), 4.12

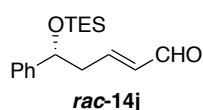
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(quintet, $J = 5.8$ Hz, 1H), 3.74 (ddd, $J = 10.6, 6.5, 5.7$ Hz, 1H), 3.68 (dt, $J = 10.5, 6.1$ Hz, 1H), 2.53 (dddd, A of ABMNX, $J_{AB} = 14.4$ Hz, $J_{AM} = 6.8$ Hz, $J_{AN} = 5.4$ Hz, $J_{AX} = 1.4$ Hz, 1H), 2.45-2.40 (m, 1H), 1.74 (dq, $J = 13.5, 6.4$ Hz, 1H), 1.64 (dq, $J = 13.6, 6.2$ Hz, 1H), 1.05 (s, 9H), 0.93 (t, $J = 8.0$ Hz, 9H), 0.69 (q, $J = 7.9$ Hz, 6H).

^{13}C NMR (125 MHz, CDCl_3) δ 194.04 (o), 155.38 (o), 135.57 (o), 134.89 (o), 133.64 (e), 133.62 (e), 129.76 (o), 129.72 (o), 127.72 (o), 127.70 (o), 68.04 (o), 60.38 (e), 40.57 (e), 39.97 (e), 26.86 (o), 19.17 (e), 6.94 (o), 4.93 (e).

IR (Neat) 2954 (m), 2876 (m), 2805 (w), 2729 (w), 1694 (s), 1638 (w), 1588 (w), 1110 (s), 1087 (vs), 977 (m), 738 (s), 702 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{29}\text{H}_{44}\text{O}_3\text{NaSi}_2$ 519.2727, found 519.2733.



(*E*)-5-Phenyl-5-(triethylsilyloxy)pent-2-enal (*rac*-1j)

The product was obtained after flash chromatography (silica gel, Et_2O /petroleum ether – 0% to 8%) in 86% yield.

Colour and state: Yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 9.47 (d, $J = 7.9$ Hz, 1H), 7.32-7.30 (m, 4H), 7.27-7.24 (m, 1H), 6.82 (dt, $J = 15.3, 7.6$ Hz, 1H), 6.09 (dd, $J = 15.7, 8.1$ Hz, 1H), 4.84 (dd, $J = 6.9, 5.0$ Hz, 1H), 2.74 (app. dt, A of ABM_2 , $J_{AB} = 14.5$ Hz, $J_{AM} = 7.2$ Hz, 1H), 2.70-2.65 (m, 1H), 0.87 (t, $J = 8.0$ Hz, 9H), 0.54 (dq, A of ABX_3 , $J_{AB} = 15.8$ Hz, $J_{AX} = 8.0$ Hz, 3H), 0.51 (dq, B of ABX_3 , $J_{AB} = 15.8$ Hz, $J_{BX} = 8.0$ Hz, 3H).

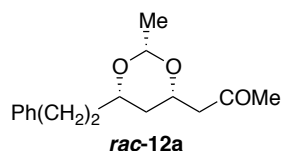
^{13}C NMR (125 MHz, CDCl_3) δ 193.86 (o), 154.71 (o), 143.99 (e), 134.89 (o), 128.32 (o), 127.56 (o), 125.68 (o), 73.58 (o), 43.98 (e), 6.75 (o), 4.76 (e).

IR (Neat) 2954 (w), 2876 (w), 2805 (w), 2729 (w), 1693 (s), 1638 (w), 1088 (m), 1068 (m), 1004 (m), 742 (m), 700 (m) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{17}\text{H}_{26}\text{O}_2\text{NaSi}$ 313.1600, found 313.1592.

2.15 Reaction of the δ -Hydroxy α,β -Unsaturated Ketones with Aliphatic Aldehydes

General Procedure: The δ -hydroxy α,β -unsaturated ketone (0.5 mmol) was dissolved in reagent grade DCM (5 mL) and stirred at room temperature. The aliphatic aldehyde (2.5 mmol, 5.0 equiv.) was added followed by bismuth(III) nitrate pentahydrate (24.3 mg, 0.05 mmol, 0.1 equiv.) and the reaction mixture stirred until consumption of the starting material (TLC control). The reaction was partitioned between DCM and saturated aqueous NaHCO₃ solution. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to afford a crude product. Purification by flash chromatography (silica gel, diethyl ether/hexanes) furnished the *syn*-1,3-dioxanes.



1-[(2*S,4*S**,6*S**)-2-Methyl-6-phenethyl-1,3-dioxan-4-yl]propan-2-one (*rac*-12a)**

Product was obtained after flash chromatography (silica gel, EtOAc/hexanes – 1:2.5) in 99% yield.

Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.30-7.26 (m, 3H), 7.20-7.17 (m, 2H), 4.71 (q, J = 5.1 Hz, 1H), 4.07 (dddd, J = 11.0, 7.4, 5.5, 2.0 Hz, 1H), 3.60 (dddd, J = 10.7, 7.7, 4.8, 2.6 Hz, 1H), 2.78 (ddd, J = 14.0, 9.4, 4.9 Hz, 1H), 2.77 (dd, A of ABX, J_{AB} = 16.3 Hz, J_{AX} = 7.0 Hz, 1H), 2.67 (ddd, B of ABXY, J_{AB} = 13.8 Hz, J_{BX} = 9.3 Hz, J_{BY} = 7.0 Hz, 1H), 2.48 (dd, B of ABX, J_{AB} = 16.3 Hz, J_{AX} = 5.6 Hz, 1H), 2.18 (s, 3H), 1.89 (dddd, A of ABMNX, J_{AB} = 13.8 Hz, J_{AM} = 9.2 Hz, J_{AN} = 8.3 Hz, J_{AX} = 5.5 Hz, 1H), 1.72 (dddd, B of ABMNX, J_{AB} = 13.9 Hz, J_{BM} = 9.5 Hz, J_{BN} = 7.0 Hz, J_{BX} = 4.5 Hz,

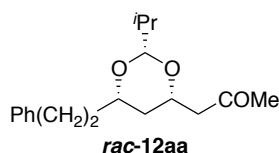
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1H), 1.58 (app. dt, $J = 13.0, 2.4$ Hz, 1H), 1.33 (d, $J = 5.1$ Hz, 3H), 1.27 (app. dt, $J = 12.8, 11.3$ Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3) δ 206.67 (e), 141.82 (e), 128.47 (o), 128.40 (o), 125.86 (o), 98.63 (o), 75.04 (o), 72.23(o), 49.50 (e), 37.37 (e), 36.51 (e), 31.16 (e), 21.14 (o).

IR (Neat) 3027 (w), 2993 (w), 2939 (w), 2864 (w), 1715 (m), 1603 (w), 1496 (w), 1362 (m), 1125 (s), 749 (m), 700 (m) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{16}\text{H}_{22}\text{O}_3\text{Na}$ 285.1467, found 285.1467.



1-[(2*S,4*S**,6*S**)-2-Isopropyl-phenethyl-1,3-dioxan-4-yl]propan-2-one (*rac*-12aa)**

Product was obtained after flash chromatography (SiO_2 , DCM) in 98% yield.

Colour and state: Colourless oil.

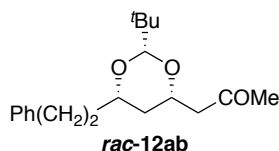
^1H NMR (500 MHz, CDCl_3) δ 7.30-7.26 (m, 2H), 7.20-7.17 (m, 3H), 4.18 (d, $J = 6.0$ Hz, 1H), 4.00 (dddd, $J = 11.0, 7.7, 5.2, 2.4$ Hz, 1H), 3.54 (dddd, $J = 11.0, 8.7, 4.0, 2.3$ Hz, 1H), 2.81-2.66 (m, 3H), 2.45 (dd, B of ABX, $J_{AB} = 15.7$ Hz, $J_{BX} = 5.2$ Hz, 1H), 2.19 (s, 3H), 1.88 (dtd, A of ABM₂X, $J_{AB} = 13.8$ Hz, $J_{AM} = 8.8$ Hz, $J_{AX} = 5.1$ Hz, 1H), 1.80 (app. dq, $J = 13.3, 6.7$ Hz, 1H), 1.71 (dddd, B of ABMNX, $J_{AB} = 13.6$ Hz, $J_{BM} = 9.3$ Hz, $J_{BN} = 7.7$ Hz, $J_{BX} = 4.2$ Hz, 1H), 1.54 (app. dt, $J = 12.9, 2.4$ Hz, 1H), 1.26 (app. dt, $J = 12.8, 11.2$ Hz, 1H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 207.19 (e), 141.93 (e), 128.53 (o), 128.37 (o), 125.82 (o), 105.50 (o), 74.72 (o), 72.62 (o), 49.62 (e), 37.41 (e), 36.97 (e), 32.83 (o), 31.23 (o), 31.11 (e), 17.44 (o), 17.40 (o).

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IR (Neat) 3027 (w), 2958 (m), 2916 (m), 2871 (m), 1716 (s), 1603 (w), 1495 (w), 1349 (m), 1124 (m), 1028 (m), 749 (w), 701 (m) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{18}\text{H}_{26}\text{O}_3\text{Na}$ 313.1780, found 313.1778.



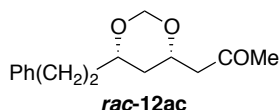
1-[(2*S,4*S**,6*S**)-2-*tert*-Butyl-6-phenethyl-1,3-dioxan-4-yl]propan-2-one (*rac*-12ab)³¹**

Product was obtained after flash chromatography (SiO_2 , $\text{Et}_2\text{O}/\text{DCM}$ – 1:40) in 90% yield.

Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl_3) δ 7.30-7.26 (m, 2H), 7.20-7.18 (m, 3H), 4.10 (s, 1H), 3.98 (dddd, $J = 10.8, 8.0, 5.2, 2.6$ Hz, 1H), 3.52 (dddd, $J = 11.2, 8.8, 3.8, 2.3$ Hz, 1H), 2.78 (ddd, A of ABMX, $J_{AB} = 13.9$ Hz, $J_{AM} = 8.8$ Hz, $J_{AX} = 5.0$ Hz, 1H), 2.74-2.65 (m, 1H), 2.70 (dd, A of ABX, $J_{AB} = 15.5$ Hz, $J_{AX} = 7.7$ Hz, 1H), 2.44 (dd, B of ABX, $J_{AB} = 15.3$ Hz, $J_{BX} = 4.9$ Hz, 1H), 2.19 (s, 3H), 1.86 (dtd, A of ABM₂X, $J_{AB} = 13.8$ Hz, $J_{AM} = 8.7$ Hz, $J_{AX} = 5.1$ Hz, 1H), 1.71 (dddd, B of ABMNX, $J_{AB} = 13.3$ Hz, $J_{BM} = 9.1$ Hz, $J_{BN} = 8.1$ Hz, $J_{BX} = 4.0$ Hz, 1H), 1.49 (app. dt, $J = 12.8, 2.4$ Hz, 1H), 1.24 (app. dt, $J = 12.6, 11.2$ Hz, 1H), 0.93 (s, 9H).

IR (Neat) 3027 (w), 2955 (m), 2867 (m), 1716 (s), 1603 (w), 1496 (w), 1360 (m), 1120 (s), 1004 (m) 748 (m), 700 (s) cm^{-1} .



1-[(4*S,6*S**)-6-Phenethyl-1,3-dioxan-4-yl]propan-2-one (*rac*-12ac)**

Product was obtained after flash chromatography (SiO_2 , $\text{Et}_2\text{O}/\text{hexanes}$ – 1:2, 1:1) in 98% yield.

Colour and state: Colourless oil.

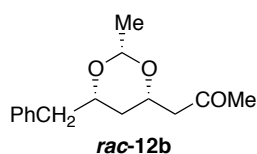
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¹H NMR (500 MHz, CDCl₃) δ 7.30-7.26 (m, 2H), 7.21-7.17 (m, 3H), 5.08 (d, $J = 6.4$ Hz, 1H), 4.71 (d, $J = 6.5$ Hz, 1H), 4.05 (dddd, $J = 10.8, 7.6, 5.2, 2.2$ Hz, 1H), 3.58 (dddd, $J = 10.8, 8.5, 4.4, 2.5$ Hz, 1H), 2.81-2.74 (m, 1H), 2.77 (dd, A of ABX, $J_{AB} = 16.3$ Hz, $J_{AX} = 7.4$ Hz, 1H), 2.67 (ddd, B of ABMX, $J_{AB} = 13.8$ Hz, $J_{BM} = 9.4$ Hz, $J_{BX} = 7.1$ Hz, 1H), 2.47 (dd, B of ABX $J_{AB} = 16.4$ Hz, $J_{BX} = 5.0$ Hz, 1H), 2.18 (s, 3H), 1.92-1.85 (m, 1H), 1.73 (dddd, $J = 13.8, 9.8, 7.0, 4.2$ Hz, 1H), 1.60 (app. dt, $J = 13.0, 2.2$ Hz, 1H), 1.39 (app. dt, $J = 13.0, 11.2$ Hz, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 206.48 (e), 141.72 (e), 128.46 (o), 128.43 (o), 125.92 (o), 93.49 (e), 75.32 (o), 72.43 (o), 49.43 (e), 37.53 (e), 37.34 (e), 31.13 (o), 31.11 (e).

IR (Neat) 3026 (w), 2994 (w), 2916 (w), 2855 (w), 1715 (s), 1603 (w), 1496 (m), 1130 (m), 1024 (s), 749 (w), 701 (m) cm⁻¹.

HRMS (CI, [M+H]⁺) calcd for C₁₅H₂₁O₃ 249.1485, found 249.1489.



1-[(2*S,4*S**,6*S**)-6-Benzyl-2-methyl-1,3-dioxan-4-yl]propan-2-one (*rac*-12b)**

Product was obtained after flash (silica gel, Et₂O/DCM – 1:50) in 97% yield.

Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.30-7.26 (m, 2H), 7.23-7.19 (m, 3H), 4.71 (q, $J = 5.1$ Hz, 1H), 4.04 (dddd, $J = 11.2, 7.4, 5.2, 2.3$ Hz, 1H), 3.84 (dddd, $J = 11.0, 8.8, 6.7, 2.4$ Hz, 1H), 2.98 (dd, A of ABX, $J_{AB} = 13.6$ Hz, $J_{AX} = 6.3$ Hz, 1H), 2.75 (dd, A of ABX, $J_{AB} = 16.3$ Hz, $J_{AX} = 7.3$ Hz, 1H), 2.67 (dd, B of ABX, $J_{AB} = 13.6$ Hz, $J_{BX} = 7.0$ Hz, 1H), 2.44 (dd, B of ABX, $J_{AB} = 16.3$ Hz, $J_{BX} = 5.2$ Hz, 1H), 2.16 (s, 3H), 1.52

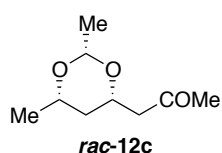
Chapter 2

(app. dt, $J = 13.0, 2.4$ Hz, 1H), 1.32 (d, $J = 5.1$ Hz, 3H), 1.26 (app. dt, $J = 12.9, 11.2$ Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3) δ 206.62 (e), 137.53 (e), 129.48 (o), 128.35 (o), 126.43 (o), 98.64 (o), 76.89 (o), 72.24 (o), 49.47 (e), 42.39 (e), 35.92 (e), 31.15 (o), 21.06 (o).

IR (Neat) 3028 (w), 2993 (w), 2915 (w), 2865 (w), 1714 (s), 1604 (w), 1495 (w), 1362 (m), 1343 (m), 1125 (s), 940 (m), 753 (m), 701 (m) cm^{-1} .

HRMS (CI, $[\text{M}+\text{NH}_4]^+$) calcd for $\text{C}_{15}\text{H}_{24}\text{NO}_3$ 266.1756, found 266.1759.



1-[(2*S,4*S**,6*S**)-2,6-Dimethyl-1,3-dioxan-4-yl]propan-2-one**
(rac-12c)

Product obtained after flash chromatography (silica gel, DCM, then $\text{Et}_2\text{O}/\text{DCM} - 1:30$) in 92% yield.

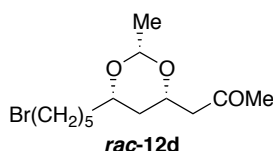
Colour and state: Yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 4.70 (q, $J = 5.1$ Hz, 1H), 4.06 (dddd, $J = 11.3, 7.4, 5.4, 2.0$ Hz, 1H), 3.74 (dq, $J = 12.5, 6.2, 2.3$ Hz, 1H), 2.74 (dd, A of ABX, $J_{AB} = 16.3$ Hz, $J_{AX} = 7.2$ Hz, 1H), 2.45 (dd, B of ABX, $J_{AB} = 16.3$ Hz, $J_{BX} = 5.5$ Hz, 1H), 2.16 (s, 3H), 1.56 (app. dt, $J = 13.0, 2.3$ Hz, 1H), 1.28 (d, $J = 5.1$ Hz, 3H), 1.20 (app. dt, $J = 12.7, 11.2$ Hz, 1H), 1.19 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 206.72 (e), 98.51 (o), 72.22 (o), 72.14 (o), 49.44 (e), 38.15 (e), 31.17 (o), 21.53 (o), 21.09 (o).

IR (Neat) 2974 (w), 2938 (w), 2869 (w), 1714 (s), 1416 (w), 1377 (m), 1362 (m), 1167 (m), 1133 (m), 958 (m), 924 (m) cm^{-1} .

HRMS (CI, $[\text{M}+\text{H}]^+$) calcd for $\text{C}_9\text{H}_{17}\text{O}_3$ 173.1178, found 173.1178.



1-[(2*S,4*S**,6*S**)-6-(5-Bromopentyl)-2-methyl-1,3-dioxan-4-yl]propan-2-one (*rac*-12d)**

Product was obtained after flash chromatography (silica gel, Et₂O/DCM – 1:30) in 99% yield.

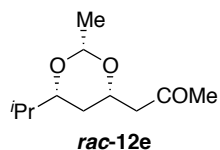
Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 4.68 (q, *J* = 5.1 Hz, 1H), 4.06 (dddd, *J* = 11.0, 7.3, 5.5, 2.0 Hz, 1H), 3.60-3.56 (m, 1H), 3.38 (t, *J* = 6.8 Hz, 2H), 2.74 (dd, A of ABX, *J*_{AB} = 16.3 Hz, *J*_{AX} = 7.1 Hz, 1H), 2.45 (dd, B of ABX, *J*_{AB} = 16.3 Hz, *J*_{BX} = 5.5 Hz, 1H), 2.16 (s, 3H), 1.83 (quintet, *J* = 7.0 Hz, 2H), 1.57-1.50 (m, 1H), 1.55 (app. dt, *J* = 12.9, 2.4 Hz, 1H), 1.48-1.29 (m, 5H), 1.27 (d, *J* = 5.1 Hz, 3H), 1.20 (app. dt, *J* = 12.8, 11.3 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 206.77 (e), 98.59 (o), 75.89 (o), 72.23 (o), 49.48 (e), 36.49 (e), 35.63 (e), 33.91 (e), 32.64 (e), 31.20 (o), 28.06 (e), 24.18 (e), 21.08 (o).

IR (Neat) 2993 (w), 2937 (m), 2861 (m), 1715 (s), 1412 (m), 1362 (m), 1128 (vs), 940 (m) cm⁻¹.

HRMS (CI, [M+H]⁺) calcd for C₁₃H₂₄BrO₃ 307.0909, found 307.0910.



1-[(2*R,4*S**,6*R**)-6-Isopropyl-2-methyl-1,3-dioxan-4-yl]propan-2-one (*rac*-12e)**

Product was obtained after flash chromatography (silica gel, DCM, then Et₂O/DCM – 1:30) in 92% yield.

Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 4.69 (q, *J* = 5.1 Hz, 1H), 4.06 (dddd, *J* = 11.1, 7.3, 5.4, 2.2 Hz, 1H), 3.29 (ddd, *J* = 11.2, 6.8, 2.3 Hz, 1H), 2.77 (dd, A of ABX, *J*_{AB} = 16.2 Hz, *J*_{AX} = 7.1 Hz, 1H), 2.48 (dd, B of ABX, *J*_{AB} = 16.2 Hz, *J*_{BX} = 5.5 Hz, 1H),

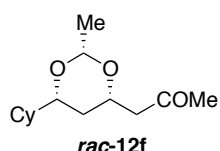
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2.18 (s, 3H), 1.68 (octet, $J = 6.8$ Hz, 1H), 1.57 (app. dt, $J = 12.8, 2.4$ Hz, 1H), 1.30 (d, $J = 5.1$ Hz, 3H), 1.21 (app. dt, $J = 12.7, 11.3$ Hz, 1H), 0.94 (d, $J = 6.7$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 206.93 (e), 98.65 (o), 81.16 (o), 72.38 (o), 49.69 (e), 33.37 (e), 32.77 (o), 31.23 (o), 21.07 (o), 18.44 (o), 17.80 (o).

IR (Neat) 2960 (m), 2874 (m), 1716 (s), 1412 (w), 1362 (m), 1119 (s), 935 (m) cm^{-1} .

HRMS (CI, $[\text{M}+\text{H}]^+$) calcd for $\text{C}_{11}\text{H}_{21}\text{O}_3$ 201.1485, found 201.1486.



1-[(2*R,4*S**,6*R**)-6-Cyclohexyl-2-methyl-1,3-dioxan-4-yl]propan-2-one (*rac*-12f)**

Product was obtained after flash chromatography (silica gel,

Et_2O /hexanes – 1:2.5) in 98% yield.

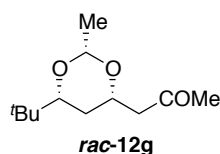
Colour and state: Colourless oil.

^1H NMR (500 MHz, CDCl_3) 4.68 (q, $J = 5.1$ Hz, 1H), 4.05 (dddd, $J = 11.1, 7.4, 5.3, 2.2$ Hz, 1H), 3.33 (ddd, $J = 11.1, 7.0, 2.2$ Hz, 1H), 2.76 (dd, A of ABX, $J_{AB} = 16.2$ Hz, $J_{AX} = 7.2$ Hz, 1H), 2.47 (dd, B of ABX, $J_{AB} = 16.1$ Hz, $J_{BX} = 5.6$ Hz, 1H), 2.18 (s, 3H), 1.91 (m, 1H), 1.73-1.63 (m, 4H), 1.56 (app. dt, $J = 12.9, 2.4$ Hz, 1H), 1.38 (dddd, $J = 14.8, 11.3, 7.2, 3.7$ Hz, 1H), 1.29 (d, $J = 5.1$ Hz, 3H), 1.26-1.08 (m, 4H), 0.98-0.89 (m, 2H).

^{13}C NMR (125 MHz, CDCl_3) δ 206.83 (e), 98.67 (o), 80.50 (o), 72.45 (o), 49.72 (e), 42.54 (o), 33.64 (e), 31.19 (o), 28.89 (e), 28.08 (e), 26.55 (e), 26.07 (e), 25.95 (e), 21.07 (o).

IR (Neat) 2919 (w), 2852 (w), 1709 (m), 1376 (m), 1364 (m), 1155 (m), 1127 (s), 1091 (m), 1068 (m), 938 (m) cm^{-1} .

HRMS (CI, $[\text{M}+\text{NH}_4]^+$) calcd for $\text{C}_{14}\text{H}_{28}\text{O}_3\text{N}$ 258.2064, found 258.2065.



1-[(2*R,4*S**,6*R**)-6-*tert*-Butyl-2-methyl-1,3-dioxan-4-yl]propan-2-one (*rac*-12g)**

Product was obtained after flash chromatography (silica gel, Et₂O/DCM – 1:9) in 95% yield.

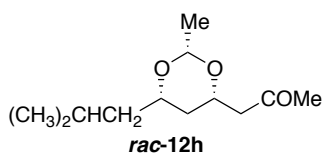
Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 4.68 (q, *J* = 5.1 Hz, 1H), 4.04 (dddd, *J* = 11.9, 6.5, 4.3, 2.2 Hz, 1H), 3.22 (dd, *J* = 11.3, 2.2 Hz, 1H), 2.77 (dd, A of ABX, *J*_{AB} = 16.1 Hz, *J*_{AX} = 7.3 Hz, 1H), 2.47 (dd, B of ABX, *J*_{AB} = 16.1 Hz, *J*_{BX} = 5.4 Hz, 1H), 2.18 (s, 3H), 1.49 (app. dt, *J* = 12.7, 2.3 Hz, 1H), 1.28 (d, *J* = 5.1 Hz, 3H), 1.26-1.21 (m, 1H), 0.88 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 206.97 (e), 98.76 (o), 83.70 (o), 72.57 (o), 46.79 (e), 33.73 (e), 31.23 (o), 33.90 (e), 25.64 (o), 21.05 (o).

IR (Neat) 2957 (w), 2871 (w), 1717 (m), 1362 (m), 1124 (s), 989 (m) cm⁻¹.

HRMS (CI, [M+H]⁺) calcd for C₁₂H₂₆NO₃N₁ 232.1907, found 232.1904.



1-[(2*S,4*S**,6*S**)-6-Isobutyl-2-methyl-1,3-dioxan-4-yl]propan-2-one (*rac*-12h)**

Product was obtained after flash chromatography (silica gel, Et₂O/DCM – 1:15) in 96% yield.

Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 4.69 (q, *J* = 5.1 Hz, 1H), 4.07 (dddd, *J* = 11.1, 7.3, 5.5, 2.1 Hz, 1H), 3.66 (dddd, *J* = 10.8, 8.1, 5.2, 2.5 Hz, 1H), 2.75 (dd, A of ABX, *J*_{AB} = 16.3 Hz, *J*_{AX} = 7.1 Hz, 1H), 2.46 (dd, B of ABX, *J*_{AB} = 16.3 Hz, *J*_{BX} = 5.5 Hz, 1H), 2.17 (s, 3H), 1.76 (d-octet, *J* = 7.6, 6.6 Hz, 1H), 1.54 (app. dt, *J* = 13.0, 2.4 Hz, 1H),

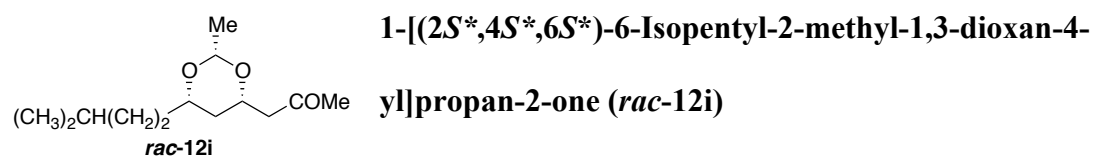
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1.48 (ddd, A of ABMX, $J_{AB} = 14.0$ Hz, $J_{AM} = 8.0$ Hz, $J_{AX} = 6.2$ Hz, 1H), 1.28 (d, $J = 5.1$ Hz, 3H), 1.22-1.15 (m, 2H), 0.88 (d, $J = 6.7$ Hz, 6H).

^{13}C NMR (125 MHz, CDCl_3) δ 206.69 (e), 98.56 (o), 74.32 (o), 72.30 (o), 49.56 (e), 44.95 (e), 36.96 (e), 31.12 (o), 23.83 (o), 23.01 (o), 22.42 (o), 21.09 (o).

IR (Neat) 2956 (m), 2870 (m), 1717 (s), 1364 (m), 1143 (s), 1115 (s), 936 (m) cm^{-1} .

HRMS (CI, $[\text{M}+\text{H}]^+$) calcd for $\text{C}_{12}\text{H}_{23}\text{O}_3$ 215.1647, found 215.1653.



Product was obtained after flash chromatography (silica gel, $\text{Et}_2\text{O}/\text{DCM} - 1:50$) in 98% yield.

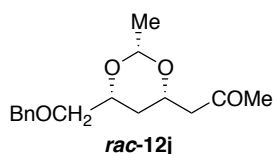
Colour and state: Yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 4.69 (q, $J = 5.1$ Hz, 1H), 4.06 (dddd, $J = 11.0, 7.3, 5.5, 2.0$ Hz, 1H), 3.55 (dddd, $J = 10.9, 8.9, 6.5, 2.1$ Hz, 1H), 2.75 (dd, A of ABX, $J_{AB} = 16.2$ Hz, $J_{AX} = 7.1$ Hz, 1H), 2.46 (dd, B of ABX, $J_{AB} = 16.2$ Hz, $J_{BX} = 5.5$ Hz, 1H), 2.17 (s, 3H), 1.60-1.52 (m, 1H), 1.57 (app. dt, $J = 13.0, 2.3$ Hz, 1H), 1.51 (nonet, $J = 6.6$ Hz, 1H), 1.40 (ddt, $J = 13.2, 11.3, 5.6$ Hz, 1H), 1.32-1.24 (m, 1H), 1.28 (d, $J = 5.1$ Hz, 3H), 1.19 (app. dt, $J = 12.8, 11.5$ Hz, 1H), 1.17-1.10 (m, 1H), 0.86 (d, $J = 6.6$ Hz, 6H).

^{13}C NMR (125 MHz, CDCl_3) δ 206.69 (e), 98.53 (o), 76.44 (o), 72.26 (o), 49.51 (e), 36.50 (e), 33.99 (e), 33.73 (e), 31.13 (o), 27.99 (o), 22.55 (o), 22.48 (o), 21.06 (o).

IR (Neat) 2954 (m), 2869 (m), 1717 (s), 1412 (m), 1365 (m), 1147 (s), 1118 (vs), 940 (m) cm^{-1} .

HRMS (CI, $[\text{M}+\text{H}]^+$) calcd for $\text{C}_{13}\text{H}_{25}\text{O}_3$ 229.1804, found 229.1805.



1-[(2*R,4*S**,6*R**)-6-(Benzyloxymethyl)-2-methyl-1,3-dioxan-4-yl]propan-2-one (*rac*-12j)**

Product was obtained after flash chromatography (silica gel, DCM/hexanes - 1:1, DCM, Et₂O/DCM – 1:20) in 96% yield.

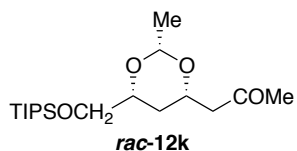
Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.35-7.26 (m, 5H), 4.75 (q, *J* = 5.1 Hz, 1H), 4.59 (d, A of AB, *J*_{AB} = 12.2 Hz, 1H), 4.54 (d, B of AB, *J*_{AB} = 12.2 Hz, 1H), 4.11 (dddd, *J* = 11.2, 7.3, 5.3, 2.2 Hz, 1H), 3.90 (dddd, *J* = 11.2, 6.4, 4.4, 2.4 Hz, 1H), 3.52 (dd, A of ABX, *J*_{AB} = 10.2 Hz, *J*_{AX} = 6.2 Hz, 1H), 3.42 (dd, B of ABX, *J*_{AB} = 10.2 Hz, *J*_{BX} = 4.2 Hz, 1H), 2.77 (dd, A of ABX, *J*_{AB} = 16.3 Hz, *J*_{AX} = 7.2 Hz, 1H), 2.47 (dd, B of ABX, *J*_{AB} = 16.3 Hz, *J*_{BX} = 5.4 Hz, 1H), 2.17 (s, 3H), 1.57 (app. dt, *J* = 12.9, 2.5 Hz, 1H), 1.33 (d, *J* = 5.1 Hz, 3H), 1.32 (app. dt, *J* = 12.8, 11.4 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 206.52 (e), 138.03 (e), 128.41 (o), 127.80 (o), 127.70 (o), 98.68 (o), 75.19 (o), 73.45 (e), 72.68 (e), 72.05 (o), 49.46 (e), 32.99 (e), 31.16 (o), 21.05 (o).

IR (Neat) 2993 (w), 2865 (m), 1714 (s), 1497 (w), 1453 (w), 1363 (m), 1135 (s), 1105 (vs), 948 (m), 740 (m) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₁₆H₂₂O₄Na 301.1416, found 301.1421.



1-[(2*R,4*S**,6*R**)-2-Methyl-6-[(triisopropylsilyloxy)methyl]-1,3-dioxan-4-yl]propan-2-one (*rac*-12k)**

Product was obtained after flash chromatography (silica gel, DCM/hexanes – 20:1, then Et₂O/DCM – 1:15) in 96% yield.

Colour and state: Colourless oil.

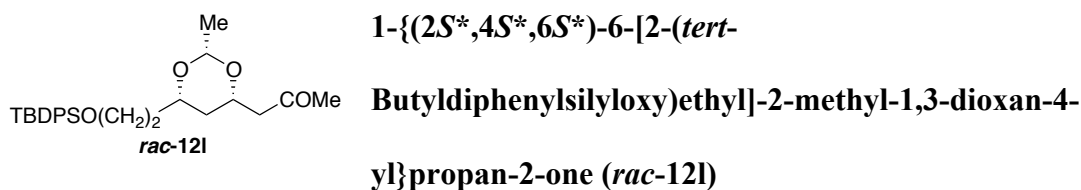
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¹H NMR (500 MHz, CDCl₃) δ 4.74 (q, *J* = 5.1 Hz, 1H), 4.12 (dddd, *J* = 11.4, 7.5, 5.0, 2.5 Hz, 1H), 3.80 (dd, A of ABX, *J*_{AB} = 9.5 Hz, *J*_{AX} = 5.3 Hz, 1H), 3.76 (dq, *J* = 11.1, 5.9, 2.3 Hz, 1H), 3.58 (dd, B of ABX, *J*_{AB} = 9.6 Hz, *J*_{BX} = 6.2 Hz, 1H), 2.78 (dd, A of ABX, *J*_{AB} = 16.2 Hz, *J*_{AX} = 7.6 Hz, 1H), 2.49 (dd, B of ABX, *J*_{AB} = 16.2 Hz, *J*_{BX} = 4.9 Hz, 1H), 2.19 (s, 3H), 1.72 (app. dt, *J* = 13.0, 2.4 Hz, 1H), 1.30-1.23 (m, 1H), 1.29 (d, *J* = 5.1 Hz, 3H), 1.11-1.03 (m, 21H).

¹³C NMR (125 MHz, CDCl₃) δ 206.71 (e), 98.48 (o), 76.62 (o), 72.25 (o), 66.30 (e), 49.61 (e), 33.60 (e), 31.19 (o), 20.99 (o), 17.95 (o), 11.91 (o).

IR (Neat) 2942 (m), 2866 (m), 1718 (m), 1463 (m), 1382 (m), 1365 (m), 1116 (vs), 882 (m), 786 (m) cm⁻¹.

HRMS (CI, [M+H]⁺) calcd for C₁₈H₃₇O₄Si 345.2461, found 345.2449.



Product was obtained after flash chromatography (silica gel, Et₂O/hexanes – 1:4) in 95% yield.

Colour and state: Yellow oil.

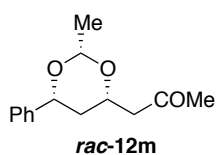
¹H NMR (500 MHz, CDCl₃) δ 7.67-7.65 (m, 4H), 7.44-7.37 (m, 6H), 4.69 (q, *J* = 5.1 Hz, 1H), 4.10 (dddd, *J* = 11.0, 7.4, 5.2, 2.2 Hz, 1H), 3.90 (dddd, *J* = 10.7, 8.0, 5.1, 2.7 Hz, 1H), 3.84 (ddd, *J* = 10.2, 8.4, 4.8 Hz, 1H), 3.72 (dt, *J* = 10.3, 5.2 Hz, 1H), 2.76 (dd, A of ABX, *J*_{AB} = 16.2 Hz, *J*_{AX} = 7.4 Hz, 1H), 2.45 (dd, B of ABX, *J*_{AB} = 16.2 Hz, *J*_{BX} = 5.2 Hz, 1H), 2.19 (s, 3H), 1.81-1.68 (m, 2H), 1.55 (dt, A of ABX, *J*_{AB} = 12.9 Hz, *J*_{AX} = 2.2 Hz, 1H), 1.28 (d, *J* = 5.1 Hz, 3H), 1.26-1.21 (m, 1H), 1.05 (s, 9H).

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^{13}C NMR (125 MHz, CDCl_3) δ 206.77 (e), 135.58 (o), 133.87 (e), 133.80 (e), 129.63 (o), 127.67 (o), 127.65 (o), 98.60 (o), 72.73 (o), 72.32 (o), 59.50 (e), 49.51 (e), 38.64 (e), 36.64 (e), 31.23 (o), 26.89 (o), 21.08 (o), 19.26 (e).

IR (Neat) 3071 (w), 3049 (w), 2931 (w), 2858 (w), 1717 (m), 1589 (w), 1428 (m), 1105 (s), 959 (m), 701 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{26}\text{H}_{36}\text{O}_4\text{NaSi}$ 463.2281, found 463.2285.



1-[(2*R,4*S**,6*R**)-2-Methyl-6-phenyl-1,3-dioxan-4-yl]propan-2-one (*rac*-12m)**

Product was obtained after flash chromatography (silica gel, DCM, $\text{Et}_2\text{O}/\text{DCM}$ – 1:50) in 97% yield.

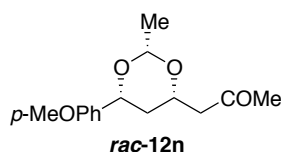
Colour and state: Colourless oil.

^1H NMR (500 MHz, CDCl_3) δ 7.37-7.26 (m, 5H), 4.93 (q, J = 5.1 Hz, 1H), 4.70 (dd, J = 11.3, 2.5 Hz, 1H), 4.27 (dddd, J = 11.0, 7.3, 5.5, 1.9 Hz, 1H), 2.83 (dd, A of ABX, J_{AB} = 16.5 Hz, J_{AX} = 7.1 Hz, 1H), 2.52 (dd, B of ABX, J_{AB} = 16.5 Hz, J_{BX} = 5.5 Hz, 1H), 2.20 (s, 3H), 1.83 (app. dt, J = 13.1, 2.4 Hz, 1H), 1.57 (app. dt, J = 13.0, 11.4 Hz, 1H), 1.40 (d, J = 5.2 Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 206.54 (e), 141.35 (e), 128.51 (o), 127.82 (o), 125.89 (o), 99.02 (o), 78.17 (o), 72.46 (o), 49.36 (e), 38.53 (e), 31.23 (o), 21.19 (o).

IR (Neat) 2993 (w), 2869 (w), 1714 (s), 1496 (w), 1369 (m), 1119 (vs), 952 (m), 700 (s) cm^{-1} .

HRMS (CI, $[\text{M}+\text{NH}_4]^+$) calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_3$ 252.1600, found 252.1608.



1-((2*R,4*S**,6*R**)-2-Methyl-6-phenyl-1,3-dioxan-4-yl)propan-2-one (*rac*-12n)**

Product was obtained after flash chromatography (silica gel, Et₂O/DCM – 1:50) in 67% yield.

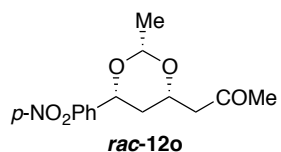
Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) 7.30-7.27 (m, 2H), 6.89-6.86 (m, 2H), 4.92 (q, *J* = 5.1 Hz, 1H), 4.64 (dd, *J* = 11.3, 2.4 Hz, 1H), 4.25 (dddd, *J* = 11.0, 7.4, 5.4, 2.0 Hz, 1H), 3.79 (s, 3H), 2.83 (dd, A of ABX, *J*_{AB} = 16.4 Hz, *J*_{AX} = 7.1 Hz, 1H), 2.52 (dd, B of ABX, *J*_{AB} = 16.4 Hz, *J*_{BX} = 5.5 Hz, 1H), 2.20 (s, 3H), 1.79 (app. dt, *J* = 13.1, 2.4 Hz, 1H), 1.58 (app. dt, *J* = 13.1, 11.2 Hz, 1H), 1.39 (d, *J* = 5.1 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 206.55 (e), 159.23 (e), 133.56 (e), 127.28 (o), 113.87 (o), 99.05 (o), 77.88 (o), 72.48 (o), 55.32 (o), 49.40 (e), 38.42 (e), 31.21 (o), 21.19 (o).

IR (Neat) 2994 (w), 2939 (w), 2837 (w), 1714 (m), 1613 (m), 1515 (m), 1411 (m), 1369 (m), 1247 (m), 1120 (s), 953 (m), 830 (m) cm⁻¹.

HRMS (CI, [M+NH₄]⁺) calcd for C₁₅H₂₄O₄N 282.1700, found 282.1696.



1-[(2*R,4*S**,6*R**)-2-Methyl-6-(4-nitrophenyl)-1,3-dioxan-4-yl]propan-2-one (*rac*-12o)**

Product was obtained after flash chromatography (silica gel, Et₂O/DCM – 1:40) in 90% yield.

Colour and state: White solid; mp 46 °C.

¹H NMR (500 MHz, CDCl₃) δ 8.20-8.17 (m, 2H), 7.54-7.50 (m, 2H), 4.93 (q, *J* = 5.1 Hz, 1H), 4.81 (dd, *J* = 11.4, 2.5 Hz, 1H), 4.28 (dtd, *J* = 11.0, 6.4, 2.1 Hz, 1H), 2.83 (dd, A of ABX, *J*_{AB} = 16.7 Hz, *J*_{AX} = 6.7 Hz, 1H), 2.53 (dd, B of ABX, *J*_{AB} = 16.7 Hz,

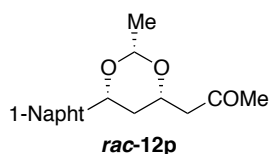
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J_{BX} = 5.9 Hz, 1H), 2.19 (s, 3H), 1.90 (app. dt, J = 13.1, 2.5 Hz, 1H), 1.46 (app. dt, J = 12.9, 11.4 Hz, 1H), 1.40 (d, J = 5.1 Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 206.16 (e), 148.67 (e), 147.33 (e), 126.44 (o), 123.72 (o), 99.01 (o), 76.86 (o), 72.21 (o), 49.13 (e), 38.33 (e), 31.14 (o), 21.05 (o).

IR (Neat) 2995 (w), 2870 (w), 1713 (m), 1602 (w), 1518 (s), 1411 (w), 1346 (s), 1116 (s), 953 (m), 855 (m), 701 (m) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_5\text{Na}$ 302.1004, found 302.0994.



1-[(2*R,4*S**,6*R**)-2-Methyl-6-(naphthalen-1-yl)-1,3-dioxan-4-yl]propan-2-one (*rac*-12p)**

Product was obtained after flash chromatography (silica gel,

Et_2O /hexanes – 1:2.5) in 99% yield.

Colour and state: Colourless oil.

^1H NMR (500 MHz, CDCl_3) δ 8.07 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 7.1 Hz, 1H), 7.54-7.47 (m, 3H), 5.43 (dd, J = 11.3, 2.1 Hz, 1H), 5.11 (q, J = 5.1 Hz, 1H), 4.42 (dddd, J = 11.0, 7.4, 5.3, 2.0 Hz, 1H), 2.85 (dd, A of ABX, J_{AB} = 16.4 Hz, J_{AX} = 7.3 Hz, 1H), 2.53 (dd, B of ABX, J_{AB} = 16.5 Hz, J_{BX} = 5.3 Hz, 1H), 2.21 (s, 3H), 2.01 (app. dt, J = 13.3, 2.3 Hz, 1H), 1.76 (app. dt, J = 13.1, 11.3 Hz, 1H), 1.48 (d, J = 5.1, 3H).

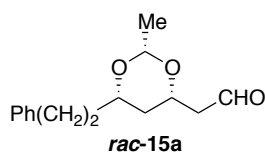
^{13}C NMR (125 MHz, CDCl_3) δ 206.49 (e), 136.83 (e), 133.80 (e), 130.10 (e), 128.96 (o), 128.29 (o), 126.14 (o), 125.59 (o), 125.55 (o), 123.47 (o), 123.04 (o), 99.34 (o), 75.59 (o), 72.68 (o), 49.35 (e), 37.78 (e), 31.25 (o), 21.29 (o).

IR (Neat) 3051 (w), 2993 (w), 2870 (w), 1713 (m), 1370 (m), 1155 (m), 1119 (s), 947 (m), 777 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{18}\text{H}_{20}\text{O}_3\text{Na}$ 307.1310, found 307.1302.

2.16 Reaction of the δ -Triethylsilyloxy α,β -Unsaturated Aldehydes with Acetaldehyde

General Procedure: The δ -triethylsilyloxy α,β -unsaturated aldehyde (0.5 mmol) was dissolved in reagent grade DCM (5 mL) and stirred at room temperature. Acetaldehyde (0.56 mL, 10 mmol, 20.0 equiv.) was added followed by bismuth(III) nitrate pentahydrate (24.3 mg, 0.05 mmol, 0.1 equiv.) and the reaction mixture stirred until consumption of the starting material (TLC control). The reaction was partitioned between DCM and saturated aqueous NaHCO₃ solution. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to afford a crude product. Purification by flash chromatography (silica gel, diethyl ether/hexanes) furnished the *syn*-1,3-dioxanes.



2-[(2*S,4*S**,6*S**)-2-Methyl-6-phenethyl-1,3-dioxan-4-yl]acetaldehyde (*rac*-15a)**

Product was obtained after flash chromatography (silica gel, DCM, Et₂O/DCM – 1:30) in 83% yield.

Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 9.80 (t, J = 1.8 Hz, 1H), 7.30-7.26 (m, 2H), 7.21-7.18 (m, 3H), 4.73 (q, J = 5.1 Hz, 1H), 4.15 (dddd, J = 11.2, 7.4, 5.0, 2.4 Hz, 1H), 3.62 (dddd, J = 10.8, 8.1, 5.1, 2.3 Hz, 1H), 2.78 (ddd, A of ABXY, J_{AB} = 14.4 Hz, J_{AX} = 9.4 Hz, J_{AY} = 5.2 Hz, 1H), 2.71 (ddd, A of ABXY, J_{AB} = 16.8 Hz, J_{AX} = 7.4 Hz, J_{AY} = 2.1 Hz, 1H), 2.71-2.65 (m, 1H), 2.52 (ddd, B of ABXY, J_{AB} = 16.8 Hz, J_{BX} = 5.1 Hz, J_{BY} = 1.5 Hz, 1H), 1.91 (dtd, A of ABM₂X, J_{AB} = 13.9 Hz, J_{AM} = 8.6 Hz, J_{AX} = 5.3 Hz, 1H), 1.74 (dddd, B of ABMN₂X, J_{AB} = 13.8 Hz, J_{BM} = 9.4 Hz, J_{BN} = 4.7 Hz, J_{BX} =

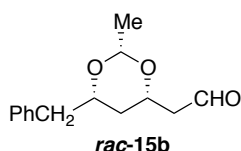
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2.4 Hz, 1H), 1.58 (app. dt, $J = 13.0, 2.4$ Hz, 1H), 1.39-1.36 (m, 1H), 1.35 (d, $J = 5.1$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 200.62 (o), 141.74 (e), 128.47 (o), 128.41 (o), 125.89 (o), 98.76 (o), 75.02 (o), 71.19 (o), 49.44 (e), 37.30 (e), 36.45 (e), 31.12 (e), 21.09 (o).

IR (Neat) 3027 (w), 2992 (w), 2940 (w), 2911 (w), 2862 (w), 2730 (w), 1724 (s), 1603 (w), 1496 (w), 1377 (m), 1340 (m), 1128 (s), 963 (m), 701 (s) cm^{-1} .

HRMS (CI, $[\text{M}+\text{NH}_4]^+$) calcd for $\text{C}_{15}\text{H}_{24}\text{NO}_3$ 266.1751, found 266.1746.



2-[(2*S,4*S**,6*S**)-2-Methyl-6-phenethyl-1,3-dioxan-4-yl]acetaldehyde (*rac*-15b)**

Product was obtained after flash chromatography (silica gel, DCM, $\text{Et}_2\text{O}/\text{DCM} - 1:30$) in 64% yield.

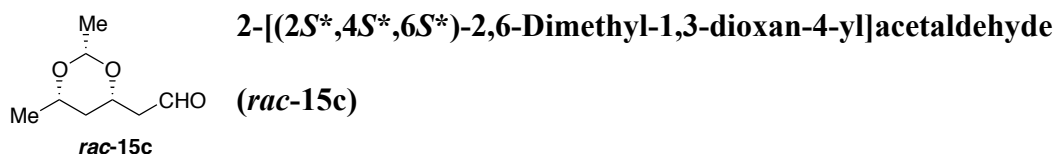
Colour and state: Colourless oil.

^1H NMR (500 MHz, CDCl_3) δ 9.77 (t, $J = 1.8$ Hz, 1H), 7.31-7.26 (m, 2H), 7.24-7.20 (m, 3H), 4.74 (q, $J = 5.1$ Hz, 1H), 4.11 (dddd, $J = 11.4, 7.4, 4.9, 2.5$ Hz, 1H), 3.85 (dddd, $J = 10.9, 8.9, 6.9, 2.2$ Hz, 1H), 3.00 (dd, A of ABX, $J_{AB} = 13.6$ Hz, $J_{AX} = 6.2$ Hz, 1H), 2.69-2.64 (m, 1H), 2.68 (dd, B of ABX, $J_{AB} = 13.2$ Hz, $J_{BX} = 6.9$ Hz, 1H), 2.48 (ddd, B of ABMX, $J_{AB} = 16.8$ Hz, $J_{BM} = 4.8$ Hz, $J_{BX} = 1.5$ Hz, 1H), 1.51 (app. dt, $J = 13.0, 2.4$ Hz, 1H), 1.38-1.31 (m, 1H), 1.33 (d, $J = 5.1$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 200.53 (o), 137.42 (e), 129.47 (o), 128.38 (o), 126.49 (o), 98.76 (o), 76.93 (o), 71.24 (o), 49.37 (e), 42.35 (e), 35.83 (e), 21.02 (o).

IR (Neat) 3029 (w), 2993 (w), 2941 (w), 2911 (w), 2864 (w), 2732 (w), 1723 (s), 1603 (w), 1496 (w), 1125 (vs), 947 (m), 701 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{14}\text{H}_{18}\text{O}_3\text{Na}$ 257.1154, found 257.1159.



Product was obtained after flash chromatography (silica gel, DCM, Et₂O:DCM – 1:50) in 56% yield.

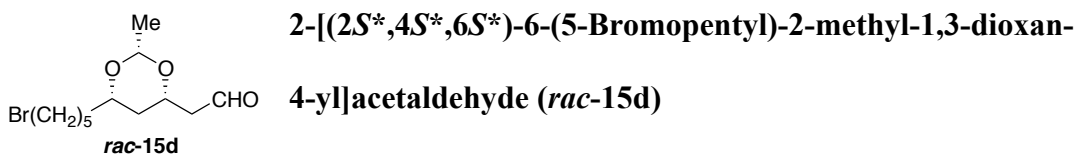
Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 9.79 (t, *J* = 1.8 Hz, 1H), 4.74 (q, *J* = 5.1 Hz, 1H), 4.16 (dddd, *J* = 11.3, 7.4, 5.0, 2.4 Hz, 1H), 3.77 (dq, *J* = 12.5, 6.2, 2.4 Hz, 1H), 2.70 (ddd, A of ABMX, *J*_{AB} = 16.9 Hz, *J*_{AM} = 7.4 Hz, *J*_{AX} = 2.1 Hz, 1H), 2.51 (ddd, B of ABMX, *J*_{AB} = 16.8 Hz, *J*_{BM} = 5.1 Hz, *J*_{BX} = 1.5 Hz, 1H), 1.58 (app. dt, *J* = 13.0, 2.4 Hz, 1H), 1.31 (d, *J* = 5.1 Hz, 3H), 1.30 (app. dt, *J* = 13.0, 11.3 Hz, 1H), 1.22 (d, *J* = 6.2 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 200.62 (o), 98.63 (o), 72.16 (o), 71.18 (o), 49.38 (e), 38.07 (e), 21.51 (o), 21.06 (o).

IR (Neat) 2911 (w), 2975 (w), 2939 (w), 2868 (w), 2730 (w), 1723 (s), 1378 (m), 1143 (vs), 957 (s), 1099 (vs) cm⁻¹.

HRMS (CI, [M+NH₄]⁺) calcd for C₈H₁₈NO₃ 176.1281, found 176.1281.



Product was obtained after flash chromatography (silica gel, DCM, Et₂O/DCM – 1:100) in 74% yield.

Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 9.79 (s, 1H), 4.72 (q, *J* = 5.1 Hz, 1H), 4.15 (dddd, *J* = 11.2, 7.4, 5.1, 2.2 Hz, 1H), 3.64-3.58 (m, 1H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.69 (ddd, A of ABMX, *J*_{AB} = 16.8 Hz, *J*_{AM} = 7.3 Hz, *J*_{AX} = 2.0 Hz, 1H), 2.52 (ddd, B of ABMX,

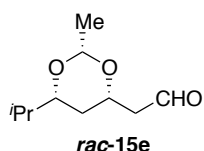
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$J_{AB} = 16.9$ Hz, $J_{BM} = 5.0$ Hz, $J_{BX} = 1.1$ Hz, 1H), 1.85 (quintet, $J = 6.9$ Hz, 2H), 1.60-1.54 (m, 1H), 1.57 (app. dt, $J = 13.1, 2.2$ Hz, 1H), 1.47-1.41 (m, 4H), 1.33-1.25 (m, 2H), 1.30 (d, $J = 5.1$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 200.66 (o), 98.71 (o), 75.91 (o), 71.21 (o), 49.44 (e), 36.44 (e), 35.59 (e), 33.87 (e), 32.63 (e), 28.04 (e), 24.17 (e), 21.04 (o).

IR (Neat) 2992 (w), 2937 (m), 2860 (m), 1724 (s), 1123 (vs), 947 (m) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{CH}_3\text{OH}+\text{Na}]^+$) calcd for $\text{C}_{13}\text{H}_{25}\text{O}_4\text{Na}^{79}\text{Br}$ 347.0834 found 347.0840.



2-[(2*R,4*S**,6*R**)-6-Isopropyl-2-methyl-1,3-dioxan-4-yl]acetaldehyde (*rac*-15e)**

Product was obtained after flash chromatography (silica gel, DCM, $\text{Et}_2\text{O}/\text{DCM}$ – 1:50) in 72% yield.

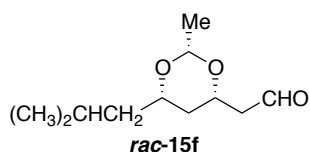
Colour and state: Colourless oil.

^1H NMR (500 MHz, C_6D_6) δ 9.52 (t, $J = 1.9$ Hz, 1H), 4.53 (q, $J = 5.1$ Hz, 1H), 3.75 (tt, $J = 7.9, 5.2$ Hz, 1H), 3.05 (dt, $J = 7.9, 6.1$ Hz, 1H), 2.35 (ddd, A of ABMX, $J_{AB} = 16.6$ Hz, $J_{AM} = 7.5$ Hz, $J_{AX} = 2.3$ Hz, 1H), 1.99 (ddd, B of ABMX, $J_{AB} = 16.5$ Hz, $J_{BM} = 4.9$ Hz, $J_{BX} = 1.6$ Hz, 1H), 1.67 (octet, $J = 6.7$ Hz, 1H), 1.39 (d, $J = 5.1$ Hz, 3H), 1.11-1.08 (m, 2H), 1.02 (d, $J = 6.7$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 198.96 (o), 98.61 (o), 80.75 (o), 71.21 (o), 49.45 (e), 33.27 (e), 32.82 (o), 21.07 (o), 18.07 (o), 17.79 (o).

IR (Neat) 2960 (m), 2873 (m), 2728 (w), 1725 (s), 1118 (vs), 993 (m) cm^{-1} .

HRMS (CI, $[\text{M}+\text{H}]^+$) calcd for $\text{C}_{10}\text{H}_{19}\text{O}_3$ 187.1329, found 187.1329.



2-[(2*S*^{*},4*S*^{*},6*S*^{*})-6-Isobutyl-2-methyl-1,3-dioxan-4-yl]acetaldehyde (*rac*-15f)

Product was obtained after flash chromatography (silica gel, DCM, Et₂O/DCM – 1:100) in 75% yield.

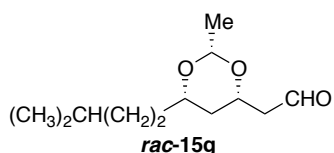
Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 9.78 (t, *J* = 1.9 Hz, 1H), 4.71 (q, *J* = 5.1 Hz, 1H), 4.15 (dddd, *J* = 11.3, 7.4, 4.9, 2.4 Hz, 1H), 3.67 (dddd, *J* = 10.8, 8.1, 5.4, 2.7 Hz, 1H), 2.67 (ddd, A of ABMX, *J*_{AB} = 16.8 Hz, *J*_{AM} = 7.4 Hz, *J*_{AX} = 2.2 Hz, 1H), 2.51 (ddd, B of ABMX, *J*_{AB} = 16.8 Hz, *J*_{BM} = 5.1 Hz, *J*_{BX} = 1.6 Hz, 1H), 1.82-1.72 (m, 1H), 1.54 (app. dt, *J* = 13.0, 2.4 Hz, 1H), 1.50 (ddd, A of ABMX, *J*_{AB} = 13.9 Hz, *J*_{AM} = 7.9 Hz, *J*_{AX} = 6.1 Hz, 1H), 1.29 (d, *J* = 5.2 Hz, 3H), 1.27 (app. dt, *J* = 13.0, 11.2 Hz, 1H), 1.20 (ddd, *J* = 13.6, 8.1, 5.2 Hz, 1H), 0.89 (dd, *J* = 6.7, 0.9 Hz, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 200.63 (o), 98.67 (o), 74.34 (o), 71.27 (o), 49.46 (e), 44.90 (e), 36.88 (e), 23.84 (o), 23.00 (o), 22.40 (o), 21.05 (o).

IR (Neat) 2995 (m), 2911 (m), 2869 (m), 2724 (w), 1725 (s), 1377 (m), 1146 (m), 1146 (s), 1118 (m) 958 (m) cm⁻¹.

HRMS (CI, [M+NH₄]⁺) calcd for C₁₁H₂₄NO₃ 218.1751, found 218.1748.



2-[(2*S*^{*},4*S*^{*},6*S*^{*})-6-Isopentyl-2-methyl-1,3-dioxan-4-yl]acetaldehyde (*rac*-15g)

Product was obtained after flash chromatography (silica gel, DCM, Et₂O/DCM – 1:100) in 72% yield.

Colour and state: Colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 9.76 (t, *J* = 1.7 Hz, 1H), 4.69 (q, *J* = 5.1 Hz, 1H), 4.12 (dddd, *J* = 11.5, 7.3, 5.0, 2.4 Hz, 1H), 3.55 (dddd, *J* = 10.9, 8.5, 6.4, 1.9 Hz,

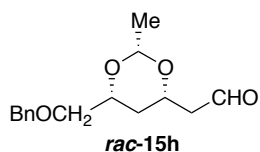
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1H), 2.66 (ddd, A of ABMX, $J_{AB} = 16.8$ Hz, $J_{AM} = 7.4$ Hz, $J_{AX} = 2.1$ Hz, 1H), 2.49 (ddd, B of ABMX, $J_{AB} = 16.8$ Hz, $J_{BM} = 5.1$ Hz, $J_{BX} = 1.5$ Hz, 1H), 1.58-1.45 (m, 1H), 1.56 (app. dt, A of ABM₂, $J_{AB} = 13.0$ Hz, $J_{AM} = 2.2$ Hz, 1H), 1.49 (septet, $J = 6.6$ Hz, 1H), 1.43-1.36 (m, 1H), 1.30-1.22 (m, 2H), 1.28 (d, $J = 5.0$ Hz, 3H), 1.11 (dddd, B of ABMNX, $J_{AB} = 13.1$ Hz, $J_{BM} = 11.8$ Hz, $J_{BN} = 6.6$ Hz, $J_{BX} = 5.2$ Hz, 1H), 0.84 (d, $J = 6.6$ Hz, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 200.61 (o), 98.65 (o), 76.46 (o), 71.24 (o), 49.44 (e), 36.45 (e), 33.98 (e), 33.69 (e), 27.99 (o), 22.54 (o), 22.48 (o), 21.03 (o).

IR (Neat) 2954 (m), 2869 (m), 2728 (w), 1726 (s), 1377 (m), 1147 (s), 1120 (s), 947 (m) cm⁻¹.

HRMS (CI, [M+NH₄]⁺) calcd for C₁₂H₂₆NO₃ 232.1907, found 232.1905.



2-[(2*R,4*S**,6*R**)-6-(Benzyloxymethyl)-2-methyl-1,3-dioxan-4-yl]acetaldehyde (*rac*-15h)**

Product was obtained after flash chromatography (silica gel,

Et₂O/hexanes – 1:1) in 72% yield.

Colour and state: Colourless oil.

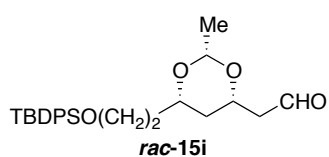
¹H NMR (500 MHz, CDCl₃) δ 9.79 (t, $J = 1.8$ Hz, 1H), 7.36-7.27 (m, 5H), 4.77 (q, $J = 5.1$ Hz, 1H), 4.60 (d, A of AB, $J_{AB} = 12.2$ Hz, 1H), 4.55 (d, B of AB, $J_{AB} = 12.2$ Hz, 1H), 4.19 (dddd, $J = 11.4, 7.5, 5.0, 2.5$ Hz, 1H), 3.92 (dddd, $J = 11.0, 6.6, 4.4, 2.2$ Hz, 1H), 3.54 (dd, A of ABX, $J_{AB} = 10.2$ Hz, $J_{AX} = 6.2$ Hz, 1H), 3.43 (dd, B of ABX, $J_{AB} = 10.2$ Hz, $J_{BX} = 4.3$ Hz, 1H), 2.71 (ddd, A of ABMX, $J_{AB} = 16.9$ Hz, $J_{AM} = 7.4$ Hz, $J_{AX} = 2.1$ Hz, 1H), 2.53 (ddd, B of ABMX, $J_{AB} = 16.9$ Hz, $J_{BM} = 5.0$ Hz, $J_{BX} = 1.5$ Hz, 1H), 1.59 (app. dt, $J = 13.0, 2.5$ Hz, 1H), 1.40 (app. dt, $J = 12.9, 11.4$ Hz, 1H), 1.34 (d, $J = 5.1$ Hz, 3H).

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^{13}C NMR (125 MHz, CDCl_3) δ 200.45 (o), 137.96 (e), 128.44 (o), 127.83 (o), 127.76 (o), 98.79 (o), 75.19 (o), 73.50 (e), 72.58 (e), 71.03 (o), 49.41 (e), 32.99 (e), 21.02 (o).

IR (Neat) 2862 (m), 2724 (w), 1722 (s), 1691 (w), 1497 (w), 1375 (m), 1139 (s), 1105 (s), 739 (vs), 949 (s), 699 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{15}\text{H}_{20}\text{O}_4\text{Na}$ 287.1259, found 287.1265.



2-[(2*S,4*S**,6*S**)-6-Isopentyl-2-methyl-1,3-dioxan-4-yl]acetaldehyde (*rac*-15i)**

Product was obtained after flash chromatography (silica gel, DCM, $\text{Et}_2\text{O}/\text{DCM}$ – 1:100) in 70% yield.

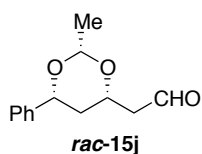
Colour and state: Colourless oil.

^1H NMR (500 MHz, CDCl_3) δ 9.81 (t, J = 1.7 Hz, 1H), 7.68-7.67 (m, 4H), 7.46-7.38 (m, 6H), 4.72 (q, J = 5.1 Hz, 1H), 4.18 (dddd, J = 11.3, 7.7, 5.0, 2.4 Hz, 1H), 3.93 (dddd, J = 10.8, 7.6, 4.6, 2.3 Hz, 1H), 3.87 (ddd, A of ABXY, J_{AB} = 10.2 Hz, J_{AX} = 8.5 Hz, J_{AY} = 4.7 Hz, 1H), 3.74 (app. dt, B of ABX₂, J_{AB} = 10.4 Hz, J_{BX} = 5.2 Hz, 1H), 2.70 (ddd, A of ABMX, J_{AB} = 16.8 Hz, J_{AM} = 7.6 Hz, J_{AX} = 2.1 Hz, 1H), 2.51 (ddd, B of ABMX, J_{AB} = 16.8 Hz, J_{BM} = 4.8 Hz, J_{BX} = 1.4 Hz, 1H), 1.84-1.70 (m, 2H), 1.56 (app. dt, J = 13.0, 2.2 Hz, 1H), 1.33 (app. dt, J = 12.8, 11.4 Hz, 1H), 1.31 (d, J = 5.1 Hz, 3H), 1.07 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ 200.77 (o), 135.60 (o), 133.83 (e), 133.76 (e), 129.70 (o), 129.69 (o), 127.72 (o), 127.70 (o), 98.73 (o), 72.73 (o), 71.27 (o), 59.43 (e), 49.43 (e), 38.59 (e), 36.54 (e), 26.91 (o), 21.08 (o), 19.29 (e).

IR (Neat) 3071 (w), 2931 (m), 2857 (m), 2729 (w), 1726 (m), 1692 (w), 1428 (m), 1105 (vs), 960 (m), 702 (s) cm^{-1} .

HRMS (ESI, $[M+Na]^+$) calcd for $C_{25}H_{34}O_4NaSi$ 449.2124, found 449.2123.



2-[(2*R,4*S**,6*R**)-6-Isopentyl-2-methyl-1,3-dioxan-4-yl]acetaldehyde (*rac*-15j)**

Product was obtained after flash chromatography (silica gel, DCM, Et₂O/DCM – 1:100) in 70% yield.

Colour and state: Colourless oil.

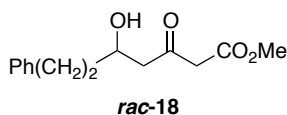
¹H NMR (500 MHz, CDCl₃) δ 9.81 (t, J = 1.8 Hz, 1H), 7.38-7.26 (m, 5H), 4.95 (q, J = 5.1 Hz, 1H), 4.71 (dd, J = 11.3, 2.5 Hz, 1H), 4.33 (dddd, J = 11.1, 7.5, 5.1, 2.3 Hz, 1H), 2.75 (ddd, A of ABMX, J_{AB} = 17.0 Hz, J_{AM} = 7.4 Hz, J_{AX} = 2.1 Hz, 1H), 2.56 (ddd, B of ABMX, J_{AB} = 17.0 Hz, J_{BM} = 5.1 Hz, J_{BX} = 1.4 Hz, 1H), 1.83 (app. dt, J = 13.2, 2.5 Hz, 1H), 1.64 (app. dt, J = 13.1, 11.3 Hz, 1H), 1.41 (d, J = 5.1 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 200.33 (o), 141.20 (e), 128.53 (o), 127.89 (o), 125.88 (o), 99.10 (o), 78.13 (o), 71.40 (o), 49.35 (e), 38.41 (e), 21.15 (o).

IR (Neat) 3032 (w), 2993 (w), 2941 (w), 2916 (w), 2862 (w), 2730 (w), 1723 (s), 1689 (w), 1497 (w), 1370 (m), 1123 (vs), 957 (m), 700 (s) cm⁻¹.

HRMS (CI, $[M+NH_4]^+$) calcd for $C_{13}H_{20}NO_3$ 238.1438, found 238.1437.

2.17 Synthesis of the Protected *anti*-1,3-Diol 22



Methyl 5-hydroxy-3-oxo-7-phenylheptanoate (*rac*-18)³²

Colour and state: Yellow oil.

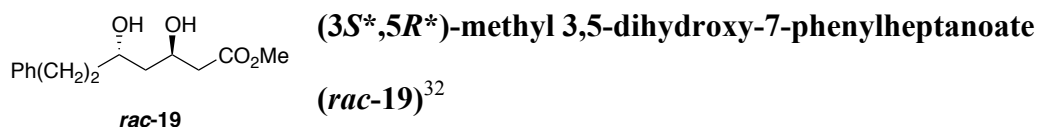
To a solution of diisopropylamine (1.86 mL, 13.15 mmol) in anhydrous THF (13 mL) at -78 °C under an atmosphere of argon was added ^{*n*}BuLi (5.1 mL, 2.5 M in hexanes, 12.8 mmol) dropwise. The solution was stirred for *ca.* 15 min at that temperature and treated with methyl acetoacetate (0.67 mL, 6.25 mmol). The

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resultant yellow solution was warmed to $-10\text{ }^{\circ}\text{C}$ for 30 min, then cooled back to $-78\text{ }^{\circ}\text{C}$, and a solution of phenylacetaldehyde **17** (0.65 mL, 5 mmol) in anhydrous THF (8 mL with washings) was added. The reaction mixture was stirred for *ca.* 30 min at $-78\text{ }^{\circ}\text{C}$ (TLC control), then quenched with AcOH and warmed to room temperature. The reaction was partitioned between saturated aqueous NH_4Cl and EtOAc. Phases were separated and the aqueous layer was washed with EtOAc (2x). The combined organic layers were washed with brine, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, EtOAc/hexanes – 1:2) afforded the unstable hydroxyl ketone **rac-18** (0.66 g, 2.65 mmol, 53% yield) as a yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 7.30-7.18 (m, 5H), 4.10-4.07 (m, 1H), 3.74 (s, 3H), 3.48 (s, 2H), 2.86 (br s, 1H), 2.84-2.66 (m, 4H), 1.87-1.68 (m, 2H).

IR (Neat) 3500 (w), 2955 (w), 1749 (s), 1715 (m), 1650 (m), 1100 (m) cm^{-1} .



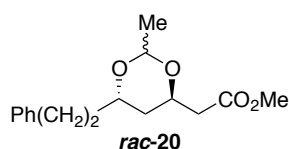
Colour and state: Colourless oil.

A solution of $^t\text{Bu}_4\text{NBH}(\text{OAc})_3$ (0.883 g, 3.36 mmol) in a mixture of anhydrous MeCN (3.5 mL) and AcOH (3.5 mL) was stirred at room temperature for 30 min under an atmosphere of argon, before it was cooled to $-40\text{ }^{\circ}\text{C}$ and treated with a solution of **rac-18** (0.2 g, 0.80 mmol) in anhydrous MeCN (7.5 mL with washings). The reaction mixture was stirred at that temperature for *ca.* 24 h (TLC control). The reaction was quenched with acetone and 1 M aqueous Rochelle salt and warmed to room temperature. The solution was partitioned between saturated aqueous NaHCO_3 and EtOAc. Phases were separated and the aqueous layer was washed with EtOAc

(2x). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, EtOAc/hexanes - 1:1.2) afforded diol **rac-19** (0.126 g, 0.501 mmol, 63% yield) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.29-7.18 (m, 5H), 4.40-4.35 (m, 1H), 3.99-3.94 (m, 1H), 3.72 (s, 3H), 2.84-2.78 (m, 2H), 2.71-2.44 (m, 4H), 1.90-1.60 (m, 4H).

IR (Neat) 3603 (w), 3509 (w), 2952 (w), 1730 (s), 1605 (m), 1175 (m) cm⁻¹.



Methyl 2-((4S*,6R*)-2-methyl-6-phenethyl-1,3-dioxan-4-yl)acetate (*rac*-20)

Colour and state: Colourless oil.

A solution of **rac-19** (0.173 g, 0.686 mmol), acetaldehyde (0.194 mL, 3.43 mmol) and PPTS (8.6 mg, 0.034 mmol) in anhydrous benzene (5 mL) was refluxed for *ca.* 24 h (TLC) under an atmosphere of argon. The reaction mixture was quenched with saturated aqueous NaHCO₃ and diluted with Et₂O. Phases were separated and the aqueous layer was washed with Et₂O (2x). The combined organic layers were dried with (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, EtOAc/hexanes – 1:2.5) afforded acetal **20** (0.059 g, 0.212 mmol, 31% yield) as a colourless oil.

The presence of diastereoisomers complicated the NMR analysis. The ¹H data of the major diastereoisomer is presented, while all observed ¹³C peaks are outlined.

¹H NMR (500 MHz, CDCl₃) δ 7.31-7.17 (m, 5H), 4.96 (q, *J* = 5.0 Hz, 1H), 4.57 (q, *J* = 7.0 Hz, 1H), 3.70-3.68 (m, 4H), 2.91 (dd, A of ABX, *J*_{AB} = 14.7 Hz, *J*_{AX} = 8.4 Hz, 1H), 2.81-2.64 (m, 1H), 2.62-2.56 (m, 1H), 2.39 (dd, B of ABX, *J*_{AB} = 14.7 Hz,

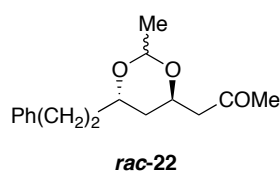
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$J_{BX} = 4.6$ Hz, 1H), 1.95-1.84 (m, 1H), 1.80-1.67 (m, 1H), 1.47-1.40 (m, 1H), 1.31 (d, $J = 5.0$ Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3) δ 171.30 (e), 141.74 (e), 141.65 (e), 128.47 (o), 128.42 (o), 128.40 (o), 125.96 (o), 125.90 (o), 125.86 (o), 98.70 (o), 92.41 (o), 91.71 (o), 98.60 (o), 75.00 (o), 72.53 (o), 71.22 (o), 60.68 (o), 68.79 (o), 68.57 (o), 51.87 (o), 51.77 (o), 41.01 (e), 40.74 (e), 37.59 (e), 37.35 (e), 36.46 (e), 36.31 (e), 33.43 (e), 33.21 (e), 32.21 (e), 32.11 (e), 31.13 (e), 21.36 (o), 21.12 (o).

IR (Neat) 2992 (w), 2948 (w), 2865 (w), 1736 (s), 1604 (w), 1120 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{16}\text{H}_{22}\text{O}_4\text{Na}$ 301.1416, found 301.1404.



1-((4*S,6*R**)-2-methyl-6-phenethyl-1,3-dioxan-4-yl)propan-2-one (*rac*-22)**

Colour and state: Colourless oil.

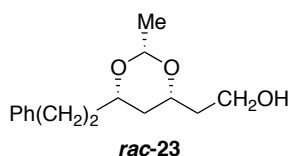
To a cooled to 0 °C mixture of **rac-20** (0.0595 g, 0.214 mmol) and Weinreb's salt (0.065 g, 0.663 mmol) in anhydrous THF (25 mL) under an atmosphere of argon was added $i\text{PrMgCl}$ (0.64 mL, 2.0 M in THF, 1.28 mmol) dropwise. The reaction mixture was stirred for *ca.* 1 h at that temperature (TLC control) and then quenched with saturated aqueous NH_4Cl . The solution was partitioned between water and Et_2O . Phases were separated and aqueous layer was washed with Et_2O (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo* to afford 0.0642 g of crude Weinreb amide **rac-21** as a colourless oil, which was used in the following step without purification.

To a cooled to 0 °C solution of crude **rac-21** (0.0642 g) in anhydrous Et_2O (2 mL) under an atmosphere of argon was added methylmagnesium bromide (0.29 mL, 3.0 M in Et_2O , 0.87 mmol) and the reaction mixture stirred at that temperature for *ca.* 30

min (TLC control). The reaction was quenched with saturated aqueous NH_4Cl and partitioned between water and DCM. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, $\text{Et}_2\text{O}/\text{DCM}$ – 0:100, 1:15) afforded methyl ketone **rac-22** (0.045 g, 0.173 mmol, 89% overall yield for 2 steps) as a colourless oil.

^1H NMR (500 MHz, CDCl_3) δ 7.30-7.17 (m, 5H), 4.92 (q, $J = 5.0$ Hz, 1H), 3.72-3.67 (m, 1H), 3.00 (dd, A of ABX, $J_{AB} = 15.7$ Hz, $J_{AX} = 7.7$ Hz, 1H), 2.80-2.62 (m, 2H), 2.44-2.39 (m, 1H), 2.18 (s, 3H), 1.95-1.66 (m, 3H), 1.43-1.37 (m, 1H), 1.29 (d, $J = 5.0$ Hz, 3H).

2.18 Deprotection of the Ethylidine Acetal



2-[(2*S,4*R**,6*S**)-2-Methyl-6-phenethyl-1,3-dioxan-4-yl]ethanol (*rac*-23)**

Colour and state: Colourless oil.

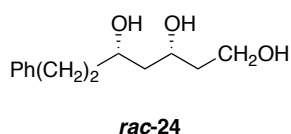
The aldehyde **rac-15a** (0.077 g, 0.309 mmol) was dissolved in anhydrous MeOH (1.5 mL) and cooled with stirring to 0 °C under an atmosphere of argon. Sodium borohydride (0.035 g, 0.928 mmol) was added and the reaction mixture was stirred at 0 °C for *ca.* 30 minutes (TLC control). The reaction was then quenched with saturated aqueous NH_4Cl and partitioned between DCM and water. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo* to afford the crude alcohol. Purification by flash chromatography (silica gel, $\text{Et}_2\text{O}/\text{hexanes}$ – 1.5:1, 2:1) to afford the primary alcohol **rac-23** (0.064 g, 0.256 mmol, 83%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.30-7.26 (m, 2H), 7.20-7.18 (m, 3H), 4.71 (q, *J* = 5.1 Hz, 1H), 3.87-3.82 (m, 1H), 3.81-3.76 (m, 2H), 3.59 (dddd, *J* = 10.8, 8.0, 5.0, 2.7 Hz, 1H), 2.78 (ddd, A of ABXY, *J*_{AB} = 14.3 Hz, *J*_{AX} = 9.2 Hz, *J*_{AY} = 5.3 Hz, 1H), 2.68 (ddd, B of ABXY, *J*_{AB} = 13.8 Hz, *J*_{BX} = 9.2 Hz, *J*_{BY} = 7.1 Hz, 1H), 2.05 (br s, 1H), 1.95-1.87 (m, 1H), 1.84-1.70 (m, 3H), 1.48 (app. dt, *J* = 13.1, 2.7 Hz, 1H), 1.41 (app. dt, *J* = 13.0, 11.0 Hz, 1H), 1.36 (d, *J* = 5.1 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 141.84 (e), 128.48 (o), 128.39 (o), 125.86 (o), 98.60 (o), 75.98 (o), 75.20 (o), 60.74 (e), 37.83 (e), 37.35 (e), 36.60 (e), 31.15 (e), 21.23 (o).

IR (Neat) 3416 (br), 3027 (w), 2987 (w), 2941 (m), 2864 (m), 1603 (w), 1496 (w), 1129 (s), 700 (m) cm⁻¹.

HRMS (CI, [M+H]⁺) calcd for C₁₅H₂₃O₃ 251.1642, found 251.1641.



(3*R,5*S**)-7-Phenylheptane-1,3,5-triol (*rac*-24)**

Colour and state: Colourless oil.

The acetal ***rac*-23** (0.077 g, 0.309 mmol) was dissolved in a mixture of MeOH and water (1.5 mL, 10:1) under an atmosphere of argon. CSA (5.0 mg, 0.022 mmol) was added and the reaction mixture was refluxed for *ca.* 100 hours (TLC control). The reaction was quenched with saturated aqueous NaHCO₃ and partitioned between DCM and water. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* for afford the crude product. Purification by flush chromatography (silica gel, Et₂O/hexanes – 19:1) afforded the triol ***rac*-24** (0.047 g, 0.294 mmol, 95%) as a colourless oil.

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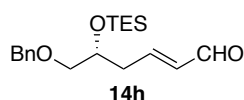
¹H NMR (500 MHz, C₆D₆) δ 7.21-7.16 (m, 4H), 7.10-7.07 (m, 1H), 4.46 (br s, 1H), 3.89-3.84 (m, 2H), 3.70-3.68 (m, 2H), 3.61-3.57 (m, 1H), 3.07 (br s, 1H), 2.75 (ddd, A of ABXY, $J_{AB} = 14.0$ Hz, $J_{AX} = 9.4$ Hz, $J_{AY} = 4.9$ Hz, 1H), 2.65 (ddd, B of ABXY, $J_{AB} = 13.7$ Hz, $J_{BX} = 9.6$ Hz, $J_{BY} = 6.8$ Hz, 1H), 1.72 (dddd, A of ABMNX, $J_{AB} = 13.4$ Hz, $J_{AM} = 9.3$ Hz, $J_{AN} = 8.0$ Hz, $J_{AX} = 5.2$ Hz, 1H), 1.61-1.46 (m, 3H), 1.41-1.35 (m, 1H), 1.16 (app. dt, B of ABM₂, $J_{AB} = 14.2$ Hz, $J_{BM} = 2.4$ Hz, 1H).

¹³C NMR (125 MHz, C₆D₆) δ 143.15 (e), 129.43 (o), 129.31 (o), 126.72 (o), 72.97 (o), 72.38 (o), 61.57 (e), 44.10 (e), 40.79 (e), 39.81 (e), 32.61 (e).

IR (Neat) 3324 (br, s), 3026 (w), 2938 (m), 2861 (m), 1603 (w), 1496 (w), 1454 (m), 1052 (vs), 698 (s) cm⁻¹.

HRMS (CI, [M+H]⁺) calcd for C₁₃H₂₁O₃ 225.1485, found 2525.1486.

2.19 Synthesis of the C18-C28 Fragment of RK-397



(*R,E*)-6-(Benzyloxy)-5-hydroxyhex-2-enal (14h)

Colour and state: Colourless oil.

Aldehyde (***R***)-**30**³³ (0.385 g, 2.00 mmol) was dissolved in anhydrous DCM (5 mL) under an atmosphere of argon. Acrolein (0.75 mL, 10.00 mmol) was added followed by Hoveyda-Grubbs 2nd generation catalyst (0.019 g, 0.030 mmol) and the mixture heated at reflux for *ca.* 4 hours (TLC control). The reaction mixture was then cooled to -78 °C and treated with 2,6-lutidine (0.58 mL, 5.00 mmol) and TESOTf (0.89 mL, 3.90 mmol) and stirred for *ca.* 10 minutes (TLC control). The reaction was quenched with saturated aqueous NaHCO₃ solution, warmed to room temperature and partitioned between water and Et₂O. Phases were separated and organic layer was washed with Et₂O (2x). The combined organic layers were successively washed with saturated aqueous NH₄Cl, water and brine, dried (MgSO₄), filtered and

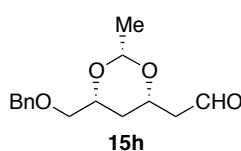
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concentrated *in vacuo* to afford a crude brown oil. Purification by flash chromatography (silica gel, 0:100 to 1:12 – Et₂O/petroleum ether) afforded the γ -triethylsilyloxy α,β -unsaturated aldehyde **14h** (0.65 g, 1.93 mmol, 98%) as a colourless oil.

$[\alpha]_{\text{D}}^{20} +7.0$ (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 9.48 (dd, *J* = 8.0, 0.4 Hz, 1H), 7.37-7.28 (m, 5H), 6.87 (dt, *J* = 15.3, 7.6 Hz, 1H), 6.15 (ddd, *J* = 15.7, 8.0, 0.8 Hz, 1H), 4.53 (d, A of AB, *J*_{AB} = 12.0 Hz, 1H), 4.50 (d, B of AB, *J*_{AB} = 12.0 Hz, 1H), 4.01 (pent, *J* = 5.6 Hz, 1H), 3.44 (dd, A of ABX, *J*_{AB} = 9.4 Hz, *J*_{AX} = 5.0 Hz, 1H), 3.34 (dd, B of ABX, *J*_{AB} = 9.4 Hz, *J*_{BX} = 6.6 Hz, 1H), 2.63 (dt, A of ABM₂, *J*_{AB} = 13.9 Hz, *J*_{AM} = 6.2 Hz, 1H), 2.54 (ddd, B of ABMX, *J*_{AB} = 14.4 Hz, *J*_{BM} = 7.6 Hz, *J*_{BX} = 6.7 Hz, 1H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.65-0.53 (m, 6H).

IR (Neat) 2954 (w), 2876 (w), 2805 (w), 2729 (w), 1691 (s), 1638 (w), 1087 (m), 977 (m), 733 (s), 698 (m) cm⁻¹.



2-[(2*R*,4*S*,6*R*)-6-(Benzyloxymethyl)-2-methyl-1,3-dioxan-4-yl]acetaldehyde (15h)

Prepared according the general procedure for the reaction of the δ -hydroxy α,β -unsaturated aldehydes with acetaldehyde in 71% yield.

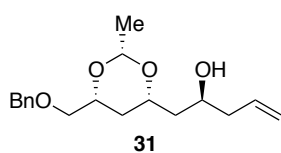
Colour and state: Colourless oil.

$[\alpha]_{\text{D}}^{20} +10.8$ (*c* 1.3, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 9.77 (s, 1H), 7.35-7.26 (m, 5H), 4.77 (q, *J* = 5.1 Hz, 1H), 4.59 (d, A of AB, *J*_{AB} = 12.2 Hz, 1H), 4.54 (d, B of AB, *J*_{AB} = 12.2 Hz, 1H), 4.19 (dddd, *J* = 11.1, 7.5, 4.8, 3.1 Hz, 1H), 3.92 (dddd, *J* = 11.0, 6.2, 4.3, 2.7 Hz, 1H), 3.53 (dd, A of ABX, *J*_{AB} = 10.2 Hz, *J*_{AX} = 6.2 Hz, 1H), 3.43 (dd, B of ABX, *J*_{AB}

= 10.2 Hz, J_{BX} = 4.3 Hz, 1H), 2.70 (ddd, A of ABMX, J_{AB} = 16.9 Hz, J_{AM} = 7.4 Hz, J_{AX} = 2.0 Hz, 1H), 2.53 (ddd, B of ABMX, J_{AB} = 16.9 Hz, J_{BM} = 5.0 Hz, J_{BX} = 1.5 Hz, 1H), 1.56 (app. dt, J = 13.0, 2.4 Hz, 1H), 1.39 (q, J = 11.4 Hz, 1H), 1.34 (d, J = 5.1 Hz, 3H).

IR (Neat) 2862 (w), 2731 (w), 1722 (m), 1139 (m), 1105 (s), 739 (m), 699 (m) cm^{-1} .



(S)-1-[(2R,4R,6R)-6-(Benzyloxymethyl)-2-methyl-1,3-dioxan-4-yl]pent-4-en-2-ol (31)

Colour and state: Colourless oil.

Titanium(IV) chloride in DCM (0.16 mL, 0.158 mmol, 1M) was diluted with anhydrous DCM (3.1 mL) and treated with $\text{Ti}(\text{O}^i\text{Pr})_4$ (0.14 mL, 0.475 mmol) at 0 °C under an atmosphere of argon. The solution stirred for *ca.* 1 hour at 0 °C, then warmed to room temperature and (*R*)-1,1'-binaphthyl-2,2'-diol (0.181 g, 0.475 mmol) was added. The reaction mixture was stirred for *ca.* 2 hours, cooled to 0 °C and then silver(I) oxide (0.073 g, 0.317 mmol) added in the absence of light. The reaction mixture was allowed to warm to room temperature and stirred for *ca.* 5 hours in dark to furnish the chiral *bis*-Ti(IV) oxide.²⁸ The catalyst was cooled to −15 °C and sequentially treated with the aldehyde **2r** (0.742 g, 3.18 mmol) in anhydrous DCM (3 mL with washings) and allyltributylstannane (1.97 mL, 6.36 mmol). The reaction was allowed to warm to 0 °C and stirred for *ca.* 48 hours (TLC control). The reaction was quenched with saturated aqueous NaHCO_3 solution and partitioned between water and Et_2O . Phases were separated and the aqueous layer was washed with Et_2O (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo* to afford the crude alcohol. Purification by flash

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chromatography (silica gel, Et₂O/hexanes – 1:1.5, 1:1) afforded the homoallylic alcohol **31** (0.849 g, 2.77 mmol, 87 %) as a colourless oil.

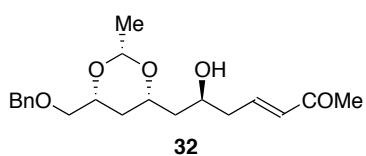
$[\alpha]_{\text{D}}^{20} +25.3$ (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.36-7.26 (m, 5H), 5.87-5.78 (m, 1H), 5.14-5.11 (m, 2H), 4.75 (q, *J* = 5.1 Hz, 1H), 4.61 (d, A of AB, *J*_{AB} = 12.2 Hz, 1H), 4.54 (d, B of AB, *J*_{AB} = 12.2 Hz, 1H), 3.99-3.93 (m, 2H), 3.90 (app. ddt, *J* = 10.1, 6.3, 4.4 Hz, 1H), 3.54 (dd, A of ABX, *J*_{AB} = 10.2 Hz, *J*_{AX} = 6.3 Hz, 1H), 3.43 (dd, B of ABX, *J*_{AB} = 10.2 Hz, *J*_{BX} = 4.3 Hz, 1H), 2.38 (d, *J* = 4.0 Hz, 1H), 2.29-2.18 (m, 2H), 1.68 (ddd, A of ABXY, *J*_{AB} = 14.5 Hz, *J*_{AX} = 8.1 Hz, *J*_{AY} = 2.8 Hz, 1H), 1.61 (ddd, B of ABXY, *J*_{AB} = 14.5 Hz, *J*_{BX} = 9.2 Hz, *J*_{BY} = 3.5 Hz, 1H), 1.48-1.41 (m, 2H), 1.36 (d, *J* = 5.1 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 138.06 (e), 134.73 (o), 128.41 (o), 127.81 (o), 127.71 (o), 117.99 (e), 98.65 (o), 75.41 (o), 73.48 (e), 73.40 (o), 72.82 (e), 67.03 (o), 42.18 (e), 41.95 (e), 33.20 (e), 21.16 (o).

IR (Neat) 3485 (br, w), 2916 (m), 2861 (m), 1641 (w), 1497 (w), 1140 (s), 1101 (vs), 948 (m), 915 (m), 737 (m), 698 (m) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₁₈H₂₆O₄Na 329.1729, found 329.1715.



(*S,E*)-7-[(2*R*,4*R*,6*R*)-6-(Benzyloxymethyl)-2-methyl-1,3-dioxan-4-yl]-6-hydroxyhept-3-en-2-one (32**)**

Colour and state: Yellow oil.

The homoallylic alcohol **31** (0.441 g, 1.438 mmol) was dissolved in anhydrous DCM (3.7 mL) under an atmosphere of argon. Methyl vinyl ketone (0.58 mL, 7.19 mmol) was added followed by Hoveyda–Grubbs 2nd generation catalyst (9.0 mg, 0.014 mmol) and the resulting mixture heated at reflux for *ca.* 2 hours (TLC control). The

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reaction mixture was concentrated *in vacuo* and purified by flash chromatography (silica gel, Et₂O/petroleum ether – 1:10, 1:8) to afford the γ -hydroxy α,β -unsaturated ketone **32** (0.435 g, 1.248 mmol, 87%) as yellow oil.

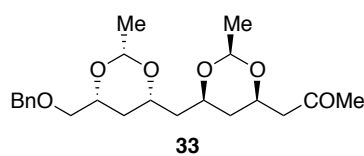
$[\alpha]_D^{20} +13.3$ (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.29-7.27 (m, 4H), 7.24-7.19 (m, 1H), 6.80 (dt, *J* = 15.9, 7.2 Hz, 1H), 6.06 (d, *J* = 16.0 Hz, 1H), 4.67 (q, *J* = 5.1 Hz, 1H), 4.53 (d, A of AB, *J*_{AB} = 12.2 Hz, 1H), 4.48 (d, B of AB, *J*_{AB} = 12.2 Hz, 1H), 4.05-3.98 (m, 1H), 3.91-3.81 (m, 1H), 3.85-3.81 (m, 1H), 3.48 (dd, A of ABX, *J*_{AB} = 10.2 Hz, *J*_{AX} = 6.2 Hz, 1H), 3.37 (dd, A of ABX, *J*_{AB} = 10.2 Hz, *J*_{BX} = 4.2 Hz, 1H), 3.21 (br s, 1H), 2.33 (app. t, *J* = 6.6 Hz, 2H), 2.18 (s, 3H), 1.63-1.54 (m, 2H), 1.41-1.35 (m, 2H), 1.29 (d, *J* = 5.1 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 198.79 (e), 144.91 (o), 137.99 (e), 133.27 (o), 128.38 (o), 127.75 (o), 127.68 (o), 98.57 (o), 75.33 (o), 73.39 (e), 73.10 (o), 72.74 (e), 66.60 (o), 42.34 (e), 40.71 (e), 33.06 (e), 26.82 (o), 21.13 (o).

IR (Neat) 3467 (br), 2864 (m), 1671 (s), 1626 (m), 1497 (w), 1363 (m), 1255 (m), 1136 (s), 1100 (vs), 978 (s), 948 (s), 738 (m), 699 (m) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₂₀H₂₈O₅Na 371.1834, found 371.1840.



1-[(2*R*,4*R*,6*R*)-6-{[(2*R*,4*R*,6*R*)-6-(Benzyloxymethyl)-2-methyl-1,3-dioxan-4-yl]methyl}-2-methyl-1,3-dioxan-4-yl]propan-2-one (33)

Colour and state: Colourless oil.

The γ -hydroxy α,β -unsaturated ketone **32** (0.458 g, 1.314 mmol) was dissolved in reagent grade DCM (13 mL) and treated with acetaldehyde (0.37 mL, 6.57 mmol) and bismuth(III) nitrate pentahydrate (64.0 mg, 0.131 mmol). The reaction mixture

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was stirred for *ca.* 24 hours at ambient temperature (TLC control) and then partitioned between DCM and saturated aqueous NaHCO₃ solution. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to afford the crude product. Purification by flash chromatography (silica gel, EtOAc/hexanes – 1:2) afforded the *bis*-acetal **33** (0.469 g, 1.194 mmol, 91%) as a colourless oil.

$[\alpha]_D^{20} +22.1$ (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, C₆D₆) δ 7.29-7.27 (m, 2H), 7.19-7.15 (m, 2H), 7.11-7.08 (m, 1H), 4.59 (q, *J* = 5.0 Hz, 1H), 4.56 (q, *J* = 5.0 Hz, 1H), 4.38 (d, A of AB, *J*_{AB} = 12.1 Hz, 1H), 4.35 (d, B of AB, *J*_{AB} = 12.2 Hz, 1H), 3.92 (dddd, *J* = 10.5, 7.6, 5.3, 2.3 Hz, 1H), 3.87-3.84 (m, 2H), 3.69 (app. dtd, *J* = 10.6, 5.2, 2.8 Hz, 1H), 3.48 (dd, A of ABX, *J*_{AB} = 9.9 Hz, *J*_{AX} = 5.7 Hz, 1H), 3.30 (dd, B of ABX, *J*_{AB} = 10.0 Hz, *J*_{BX} = 4.8 Hz, 1H), 2.38 (dd, A of ABX, *J*_{AB} = 16.0 Hz, *J*_{AX} = 7.3 Hz, 1H), 1.96 (dd, B of ABX, *J*_{AB} = 16.0 Hz, *J*_{BX} = 5.1 Hz, 1H), 1.70 (s, 3H), 1.53 (app. t, *J* = 6.1 Hz, 2H), 1.39 (d, *J* = 5.0 Hz, 3H), 1.31 (d, *J* = 5.1 Hz, 3H), 1.30-1.15 (m, 3H), 1.05 (app. dt, *J* = 12.5, 11.3 Hz, 1H).

¹³C NMR (125 MHz, C₆D₆) δ 204.41 (e), 139.12 (e), 128.57 (o), 127.84 (o), 127.72 (o), 98.69 (o), 98.67 (o), 75.65 (o), 73.48 (e), 72.49 (o), 72.08 (o), 72.07 (o), 49.40 (e), 43.34 (e), 37.37 (e), 34.51 (e), 30.58 (o), 21.55 (o), 21.45 (o).

IR (Neat) 2992 (w), 2940 (w), 2913 (w), 2866 (m), 1716 (m), 1497 (w), 1364 (m), 1125 (s), 117 (vs), 1030 (m), 942 (s), 739 (m), 699 (m) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₂₂H₃₂O₆Na 415.2097, found 415.2093.

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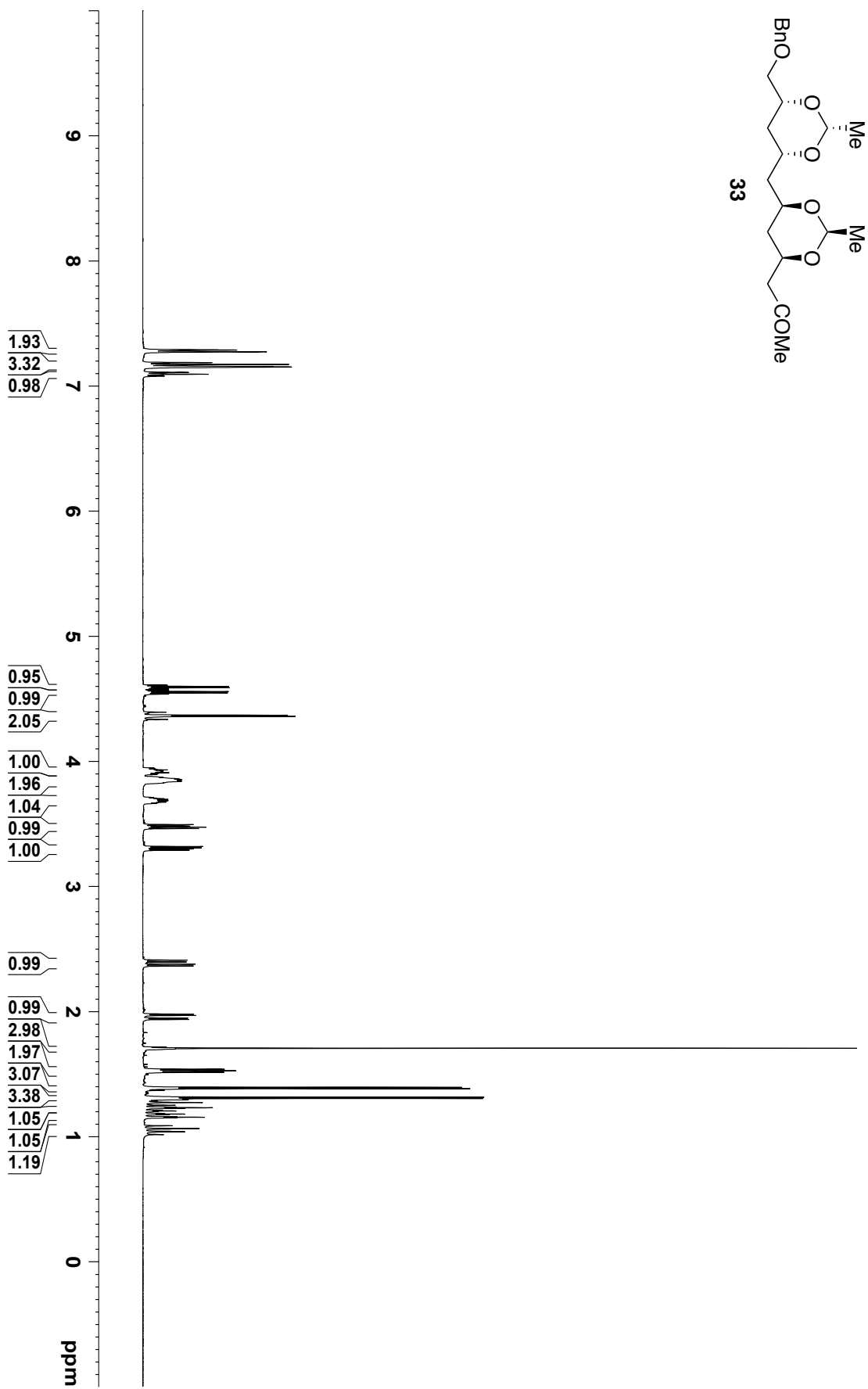
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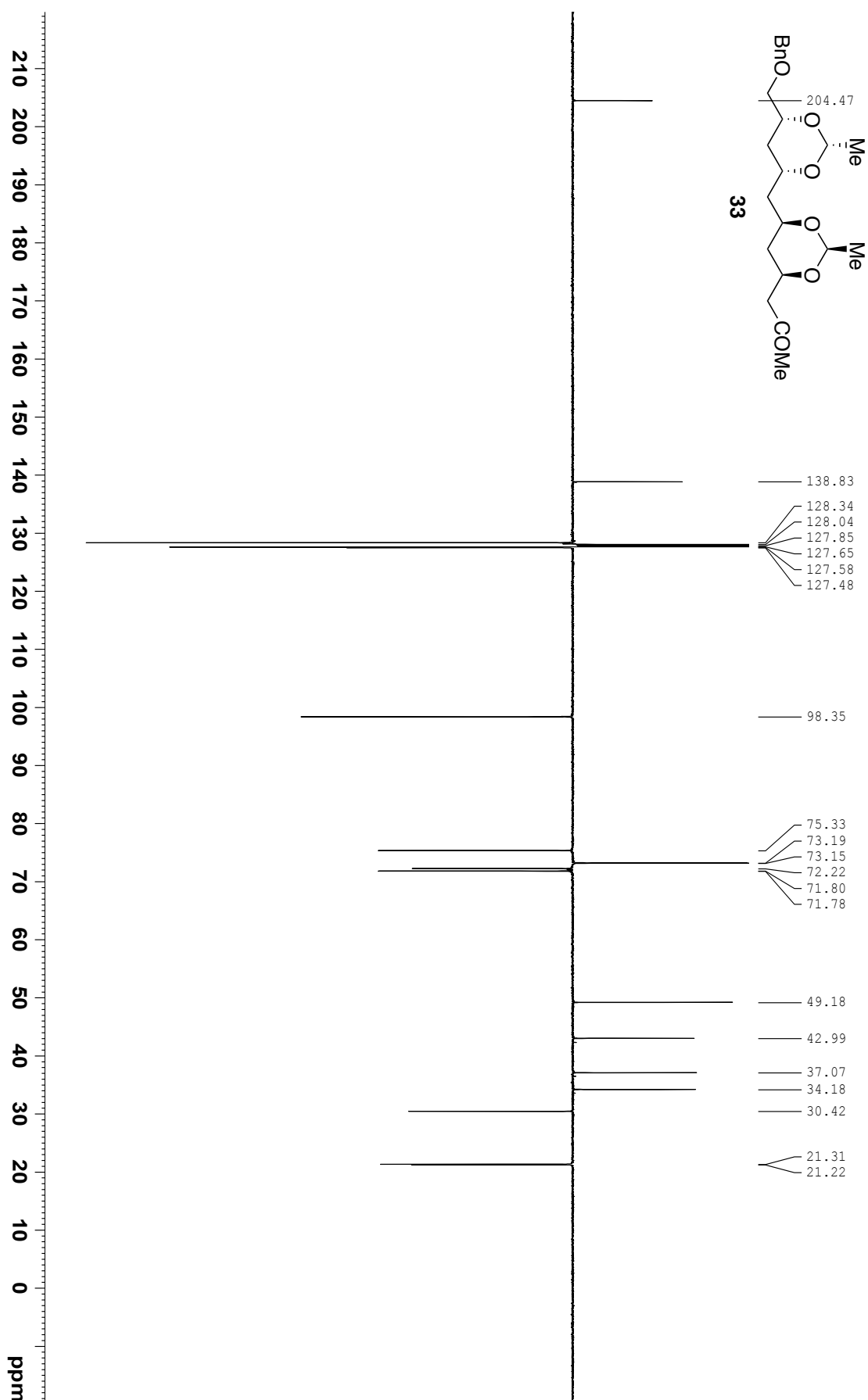
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2.21 Appendix A. ^1H and APT Spectrums for Compound 33



Chapter 3

Dinoflagellate Derived Polyketides and Synthetic Studies of the Polyol Fragment of Amphidinol 3

3.1 Introduction to Marine Dinoflagellates

Marine dinoflagellates are primitive unicellular algae known for being an abundant source of secondary metabolites with diversified structures and significant biological activities (Figure 3.1.1); *e.g.* brevetoxins (a voltage-sensitive Na⁺ channel activators),¹ okadaic acid (protein phosphatase inhibitor),² ciguatoxins (Na⁺ channel activators)³ and maitotoxin (Ca²⁺ influx stimulator).⁴

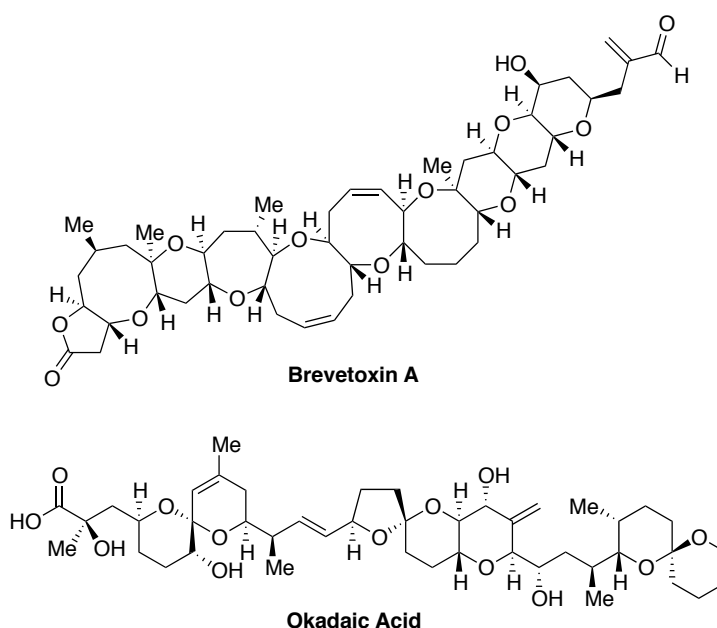


Figure 3.1.1: Structures of Selected Marine Natural Products

With more than 4000 species of marine protists reported to date, the biological activities of their secondary metabolites are extremely diverse ranging from anticancer agents to deadly neurotoxins.⁵ Although the phytoplankton is harmless, its large collections (algal blooms) can cause adverse effects on the ecosystem, tourism, fishing and shellfish industries due to vast production of these

metabolites.⁶ The cause of algal blooms is attributed to both non- and anthropogenic factors, *e.g.* a lot of sunshine, a calm sea, temperature raises, increased nitrogen and phosphorus content (run-off from fields), high iron concentration and others.⁷

Generally, four syndromes, neurotoxic shellfish poisoning (NSP), ciguatera fish poisoning (CFP), diarrhetic shellfish poisoning (DSP) and azaspiracid shellfish poisoning (AZP) result from consumption of fish or shellfish contaminated with one or more of the dinoflagellate derived polyketides. Although the latter are mainly found in bacteria, fungi and plants, only around 25 of 4000 dinoflagellate species are known sources of polyketides. Based on their structural features, these products can be organised into three categories: polyether ladders, macrocycles (including macrolides and non-macrolides) and linear polyethers.⁸

3.2 Ladder Polyether Polyketides

The first group of ladder polyethers is regarded to be the most prominent family of polyketides. It includes molecules with multiple five-, six-, seven-, eight-, and nine-membered cyclic ethers fused in a *trans-syn-trans* arrangement at the top and bottom of the structure (*e.g.* gambierol, gambieric acids, yessotoxin) (Figure 3.2.1). Customarily, ring systems in these products consist of 4 to 32 fused cycles with ring junctions substituted by either a hydrogen atom or a methyl group.

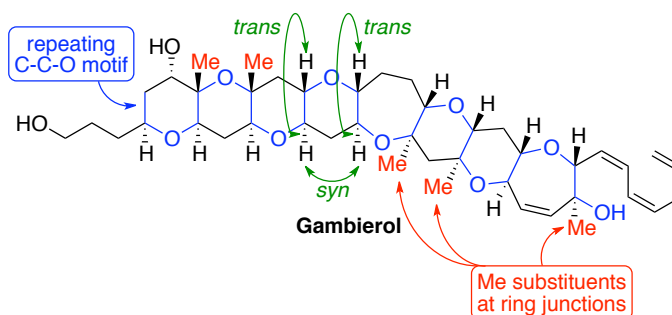


Figure 3.2.1: Structure of Gambierol and its Structural Elements

The repeating C-C-O sequence can be traced along the molecule, which suggests the plausible biosynthetic pathway to these polyketides, originating from the epoxide-opening cascades, as independently hypothesised by Nakanishi and Shimizu.⁹

3.3 Macroyclic Polyketides

Macrocycles are the second largest category of the marine dinoflagellate polyketides. In total, 34 cytotoxic macrolides, designated amphidinolides, have been isolated from seven strains of the laboratory-cultured *Amphidinium sp.* protists symbiotic with the Okinawan marine flatworms, *Amphiscolops sp.* (Figure 3.3.1).^{5a} A large collection of amphidinolides A-E, J, K, M-S, V were extracted from the Y-5 strain. Another three amphidinolides: G, H, L were gathered from the Y-25 strain, while Y-26 afforded amphidinolide F in conjunction with B and C.

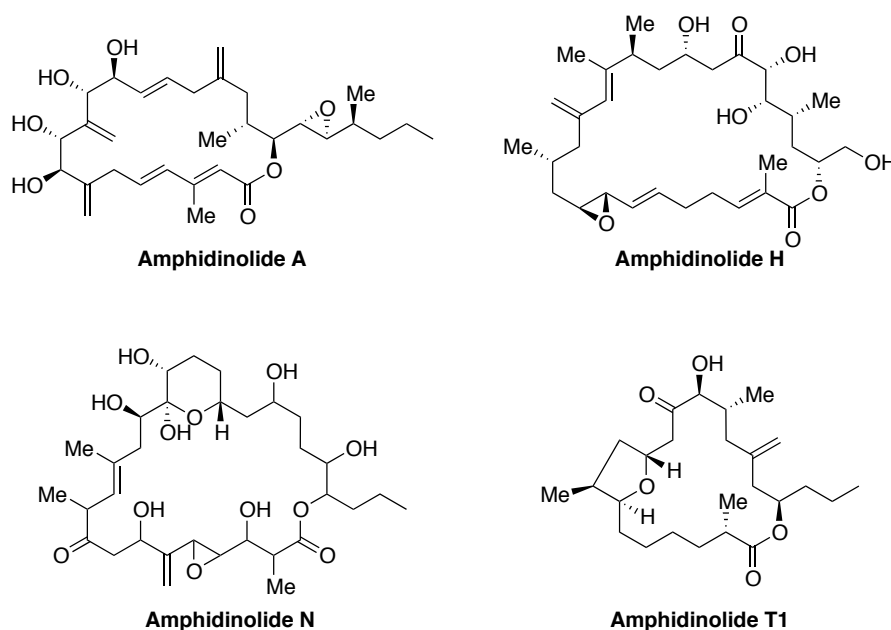


Figure 3.3.1: Structures of Selected Amphidinolides

Amphidinolides T1, T3-T5, U, B, C were isolated from Y-56. The Y-71 strain furnished one new amphidinolide, T2, with the already known T1, B, C, F.

Lastly, extraction from the Y-72 strain afforded G, H; whereas Y-42 gave G2, G3, H2-H5 and W-Y congeners.

The common feature of all amphidinolides is the presence of a 12 to 29-membered macrocyclic lactone ring. Additionally, multiple sites of unsaturation are often present in the molecule (*exo*-methylene units, 1,2-di- and 1,1,2-trisubstituted alkenes), in affiliation with oxacycles such as epoxides, furans and pyrans. It is noteworthy that more than half of the amphidinolides possess an odd-numbered macrocyclic lactone, which is in great contrast to the macrolide antibiotics isolated from the terrestrial microorganisms, which contain even-numbered rings. To address this issue, biosynthesis of amphidinolides J,¹⁰ G and H¹¹ were studied in great detail.

The remarkably strong cytotoxic activity against various tumor cells makes these compounds potential cancer drugs, *e.g.* the most active amphidinolide, N, displays *nano*- and *picomolar* cytotoxicity against L1210 cells ($IC_{50} = 0.05$ ng/mL) and KB cells ($IC_{50} = 0.06$ ng/mL).¹² The unique structural features, impressive biological properties in conjunction with limited natural occurrence have encouraged the synthetic community to synthesise various members of the family.¹³

Several related macrolides, the pectenotoxins (PTXs),¹⁴ have been isolated from scallops and greenshell mussels and were later found in the dinoflagellate *Dinophysis fortii* (Figure 3.3.2).

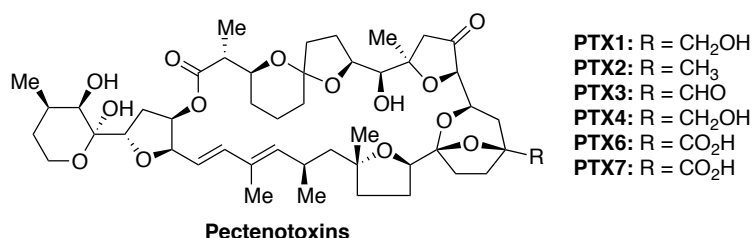


Figure 3.3.2: Structures of Pectenotoxins

These natural products have been associated with DSP poisoning symptoms and have shown potent cytotoxicity against human lung, colon and breast cancer cell lines.

Prorocentrolides,¹⁵ pinnatoxins¹⁶ and spirolides¹⁷ are other remarkable groups of macrocyclic secondary metabolites that have a distinctive cyclic imine moiety in their structures (Figure 3.3.3). The first family of compounds are dinoflagellate-derived and were isolated from *Prorocentrum sp.*, while the last two were extracted from scallops and mussels. The activity evaluation in mouse bioassays described them as fast-acting toxins. Notably, investigation of the reduced amine form of these products suggested that the imine functionality is responsible for the observed toxicities.¹⁸

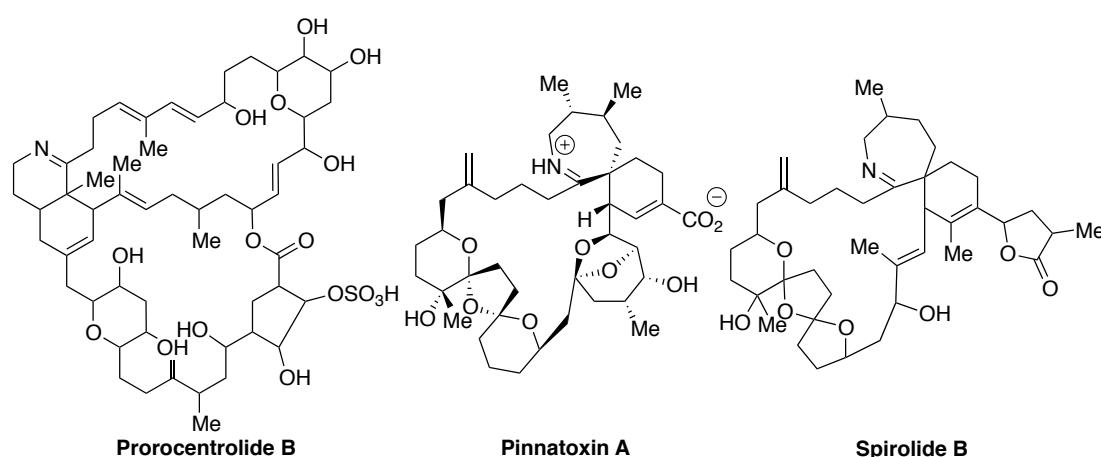


Figure 3.3.3: Structures of Marine Cyclic Imine Toxins

3.4 Linear Polyethers

The last group of dinoflagellate-derived polyketides are linear polyethers. Structurally, these natural products could be assumed to be open forms of macrocyclic polyketides, formed *via* hydrolysis (*vide supra*). Okadaic acid (OA) is a remarkable example of this type of secondary metabolite, which was isolated from the sponge *Halichondria sp.*, as well as dinoflagellates *Prorocentrum sp.* and

Dinophysis sp. (Figure 3.4.1).^{2,19} This natural product is known for its unique structural features and biological profile. The biosynthesis of OA proceeds *via* an unusual route involving both carbon backbone formation²⁰ and cyclisation.²¹ In addition, okadaic acid is associated with DSP²² and expresses highly selective inhibition of protein phosphatases.^{2c}

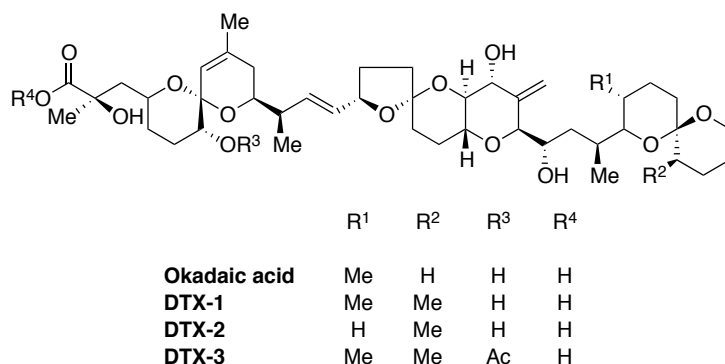


Figure 3.4.1: Structures of OA and DTX Toxins

A family of related polyethers, dinophysis toxins (DTX-1-5, 5a, acanthafolicin) was isolated from the same dinoflagellate source as OA (Figure 3.4.1).¹⁹ Similarly, these polyketides are inhibitors of protein phosphatases PP-1, PP-2A and potent tumour promoters.²³

3.5 Background of Amphidinols

Amphidinols (AMs) and their related congeners are polyene-polyhydroxy compounds, belonging to the linear polyether family, which were isolated from *Amphidinium* sp. strains. Their structures are characterised by the skipped polyene chain, two or three densely substituted tetrahydropyrans (THP) and a linear polyhydroxyl moiety (Figure 3.5.2 and Figure 3.5.3).

The first member of the family (AM1) was sequestered from *Amphidinium klebsii*, collected at Ishigaki Island, Japan, by the group of Naoki and Yasumoto in

1991, and the structure was elucidated by the same group.²⁴ Tachibana and co-workers isolated and subsequently determined the structure of amphidinol 2, which was extracted from *A. klebsii*, gathered at Aburatsubo Bay in Miura Peninsula, Japan in 1995.²⁵ Amphidinol 3 was the third congener isolated from *A. klebsii* by Murata and co-workers in 1997 (Figure 3.5.1).²⁶ Notably, it became the first molecule in the family to have its absolute configuration deduced using a combination of *J*-based configurational analysis (JBCA) for acyclic 1,2- and 1,3-dioxygenated systems,²⁷ the modified Mosher's method,²⁸ nOe experiments and chiral HPLC analysis of degradation products. In 2008, Oishi and Murata revised the original structure of AM3 and reassigned the absolute configuration of the C2 stereocentre.⁹² Later, the same group reasserted the absolute configuration at C50-C51, which remained ambiguous until that time.²⁹

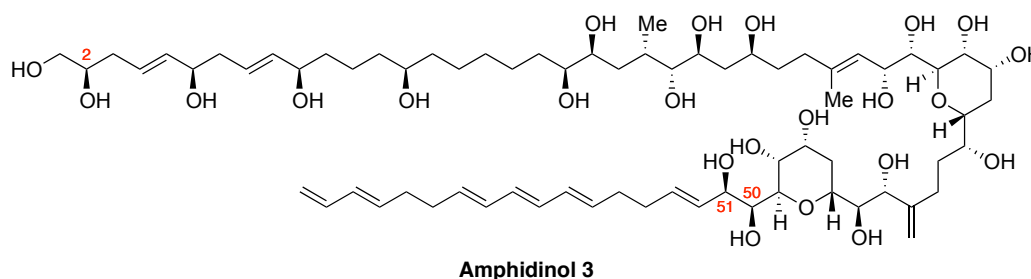


Figure 3.5.1: Structure and Absolute Configuration of Amphidinol 3

Subsequently, isolation and structural elucidation of other congeners in the family was carried out. AM4-AM8³⁰ and AM14, AM15³¹ homologs were gathered from *A. klebsii*; AM9-A13, AM2, AM4³² were found in *A. carterae*, collected at Kauaroa, the South Island, New Zealand and AM17³³ was isolated from *A. carterae*, found at Little San Salvador Island, Bahamas.

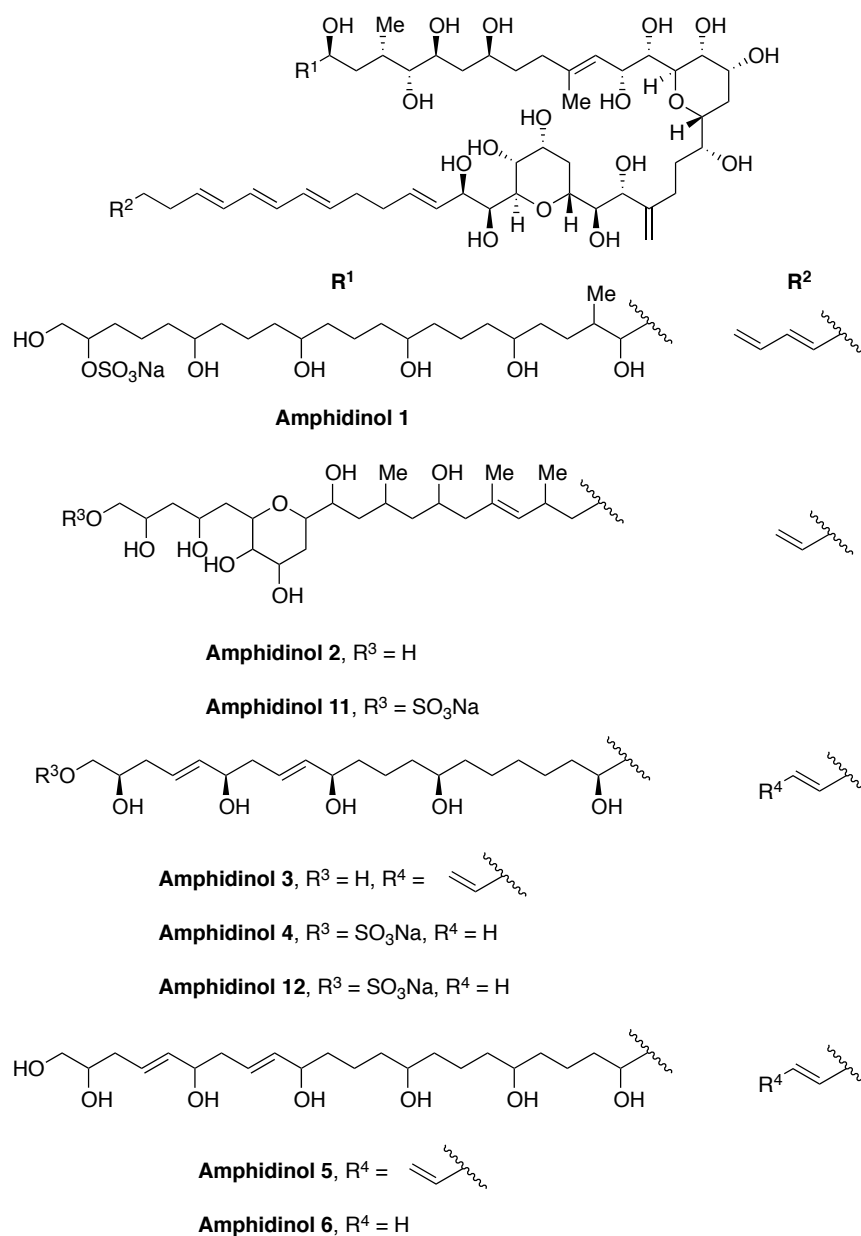


Figure 3.5.2: Structures of Amphidinols Isolated from *Amphidinium* sp.

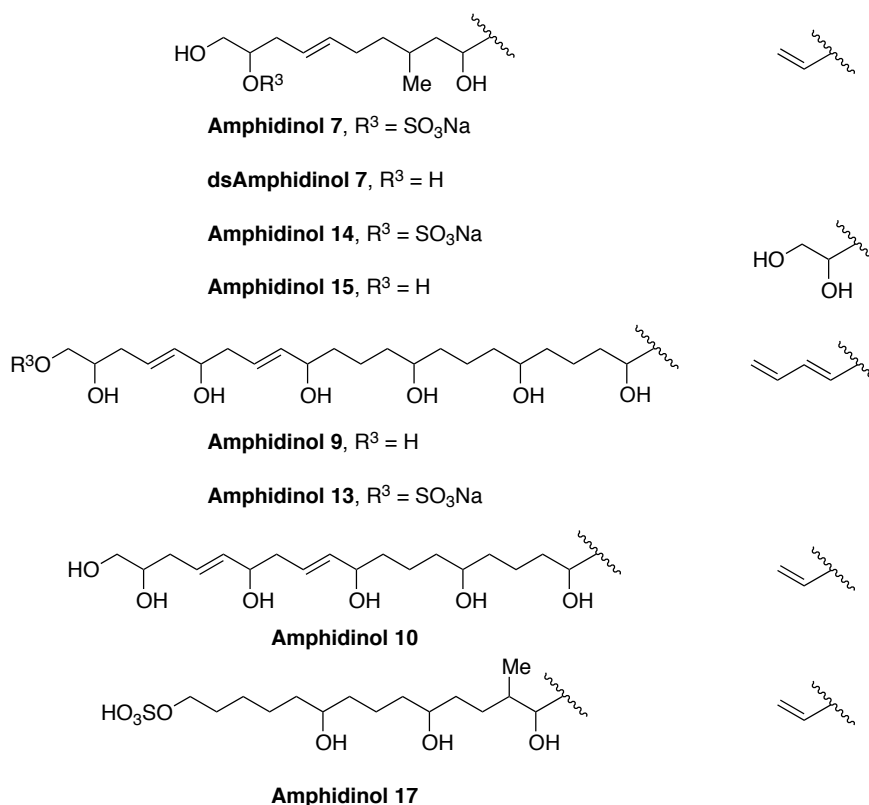


Figure 3.5.3: Structures of Amphidinols Isolated from *Amphidinium* sp. (Cont.)

3.6 Biological Activity of Amphidinols

The family of amphidinols largely exhibits strong antifungal, cytotoxic, haemolytic and diatom activities. Their potent membrane permeabilising action is associated with unique structural features and is very specific for having a non-detergent mechanism.³⁴ In studies conducted by Murata and co-workers, antifungal and haemolytic activities of amphidinol homologs were compared with those of known polyene antibiotics, amphotericin B (AmB) and filipin III (Table 3.6.1).^{34a,b} The latter compounds were chosen since both of them have a structure reminiscent to the AMs, which is comprised of isolated polyolefinic and polyhydroxyl chains.

Table 3.6.1: *Haemolytic and Antifungal Activities of Amphidinols and Other Polyene Antibiotics*

Compound	Antifungal activity (MEC in µg/disk) ^a	Haemolysis (EC ₅₀ in µM) ^b	Cytotoxicity (µg/mL) ^c
AM1	6	0.05	-
AM2	6-44.3	1.2-1.7	14.8
AM3	4-9	0.009-0.4	-
AM4	6-58.2	0.21	25.3
AM6	6	0.19-2.9	-
AM5	6	0.23	-
AM6	6	0.58	-
AM7	10	3	-
dsAM7^d	8	1.2	-
AM9	32.9	0.18	36.5
AM10	154.0	6.53	35.2
AM11	256.6	28.9	23.0
AM12	>100	2.99	26.8
AM13	132.0	2.02	32.5
AM14	>60	>50	-
AM15	60	>50	-
AM17	n/a ^e	4.9	-
AmB	6.3	2.0	-
Filipin III	1.4	2.0	-

^aMinimal effective concentration in µg/disk against the fungi *Aspergillus niger*. ^bEC₅₀ in µM against human erythrocyte cells. ^cCytotoxicity in µg/mL against mouse lymphoid D₁ cells. ^dDesulfated amphidinol 7. ^eNo detectable activity.

The structural alterations within the amphidinol family have a characteristic impact on their biological profile.³⁴ Amphidinols do vary in size and the main divergence occurs on the termini of the polyolefin moiety and in the linear polyol fragment (Figure 3.5.2 and Figure 3.5.3). The structure-activity relationship analysis showed that the hydrophobicity of the polyene chain of AMs has a strong effect on

the membrane disruption. For example, AM14 and AM15 homologs possessing the hydrophilic dihydroxyl group on the polyene show greatly reduced biological activities in comparison with non-hydroxylated analogs.³¹ The presence of the sulfate group on the linear polyol impairs the antifungal and haemolytic activity (AM2 vs. AM11 and AM7 vs. dsAM7), albeit does not have much influence on the size of the pores/lesions formed.^{31,32b} Lastly, the length of the polyol chain has a moderate effect on the activity, in which amphidinols with the shorter side chains generally exhibit weaker bioactivity (AM3 vs. AM7).^{30b}

The studies conducted by the Murata group showed that AM3 forms ion-permeable toroidal pores/lesions, with a diameter of 2.0-2.9 nm, by binding to the phospholipid membrane with the polyene part of the molecule (C52-C67), while the hydrophilic region (C20-C51) adopts a hairpin-shaped conformation stabilised by hydrogen bonding (Figure 3.6.1).^{34b,34f,h} This explains the haemolytic activity of amphidinols, as pore formation in erythrocytes leads to their invagination and eventually to the release of haemoglobin. In contrast to AmB lesions (0.8 nm), the size of pores made by AM3 is larger and the mechanism of action is attributed to be either damage or channel-type, depending on the agent concentration.^{34a}

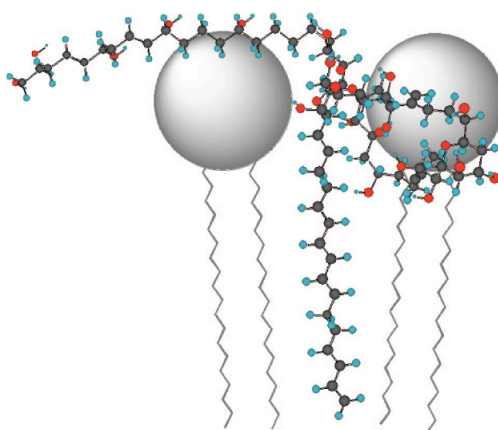


Figure 3.6.1: *Hypothetical Model of the Membrane-Bound Structure of AM3*

Subsequently, Murata and Aimoto *et al.* reported that membrane proteins (*e.g.* glycophorin A (GpA) in erythrocytes) could greatly enhance AM3-induced membrane permeability.^{34d} Another important finding was that cholesterol and ergosterol significantly increase the affinity of AM3 to the phospholipid membranes (up to 5300 times) presumably by making a stronger complex. These findings account for the absence of anti-bacterial activity of AM3, which is due the unavailability of sterols in bacterial membranes.^{34e,g,i}

3.7 Other Amphidinol Homologues

Marine microorganisms produce various bioactive secondary metabolites that have close similarities to amphidinols. The remarkable feature of the majority of these compounds is their worldwide distribution, which is in a great contrast to AMs that are mainly found in waters of Japan and Australia.

In 1997, Kobayashi and co-workers investigated secondary metabolites isolated from the another strain of *Amphidinium sp.* (Y-52), found inside cells of the marine acoel flatworm *Pseudaphanostoma luteocoloris*, gathered in Okinawa. Subsequently, they reported a series of linear carbon-chain polyols, luteophanols A-D (Figure 3.7.1).³⁵

Although these compounds have substantial structural similarities with the amphidinols, the former have a hydrophilic diene chain at C54-C60, while the latter contain a hydrophobic triene. As a result, luteophanols exhibit no antifungal activity, however they have weak antimicrobial action against Gram-positive bacteria (MIC values: *Staphylococcus aureus*, 33 µg/mL; *Sarcina lutea* 33 µg/mL; *Bacillus subtilis*, 66 µg/mL).^{35b}

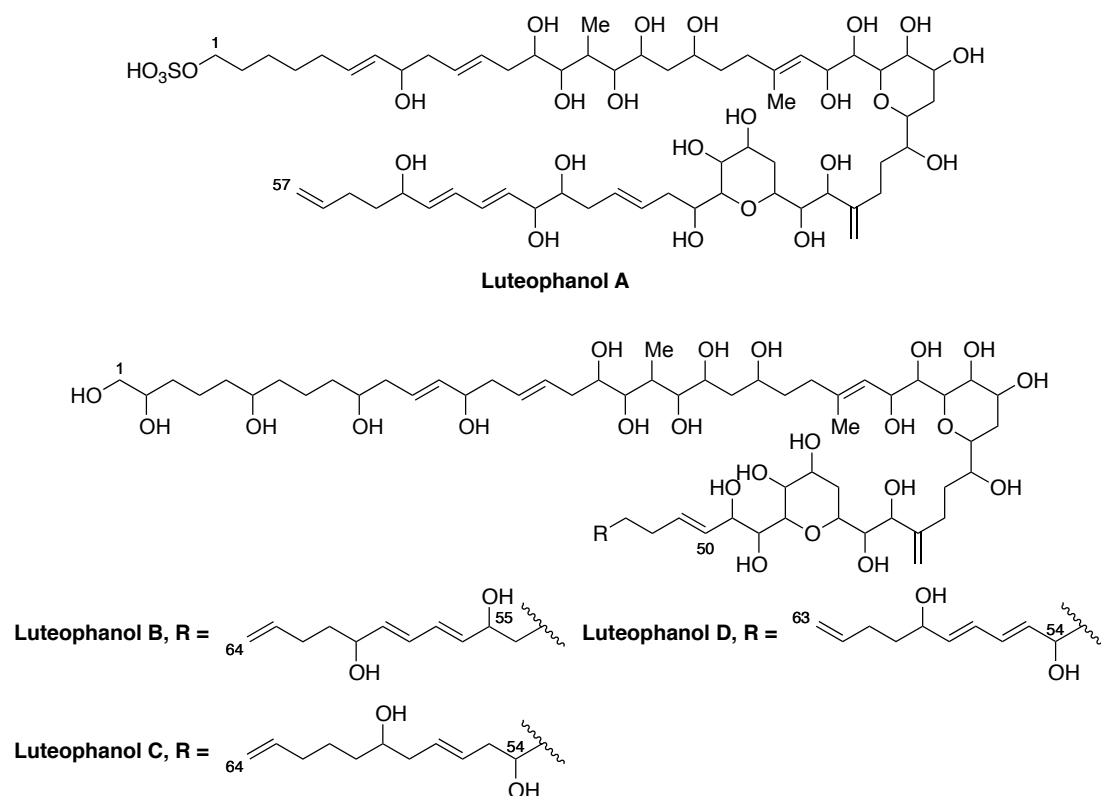


Figure 3.7.1: Structures of Luteophanols A-D

Karlotoxins (KmTx) are amphidinol-like compounds, which have haemolytic, antifungal and ichthyotoxic activities and were isolated from dinoflagellate *Karlodinium veneficum* (Figure 3.7.2).³⁶ This alga, initially named as *Gymnodinium*, was first gathered in Walvis Bay, Namibia³⁷ and the English Channel,³⁸ in 1950, and has been associated with fish kills worldwide.³⁹ Subsequently, toxins related to this dinoflagellate were detected in the clonal isolates collected from waters of Maryland, North and South Carolina, Georgia, Florida, Mississippi, New Zealand and Norway amongst others.⁴⁰

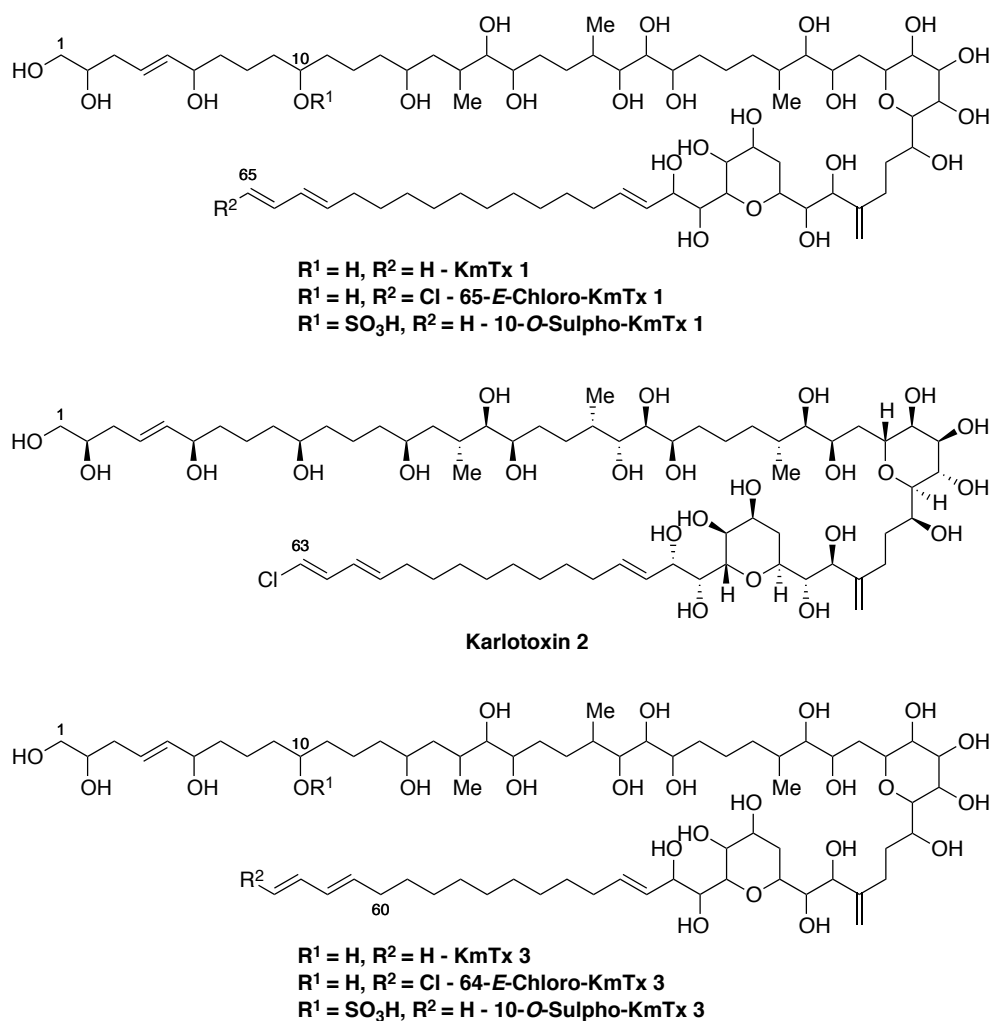


Figure 3.7.2: Structures of the Karlotoxin Family Polyols

In total, three families of karlotoxins, corresponding to KmTx 1,⁴¹ KmTx 2⁴² and KmTx 3⁴³ groups, were isolated and structurally elucidated. In 2010, Hamann and co-workers reported the structural assignment and absolute configuration of KmTx 2.⁴⁴ The main difference between groups of KmTx toxins is the length of the lipophilic side chain, which attributes to alterations in the UV absorbance maxima, potency and geographic distribution.^{39a} These structural variations were shown to have a pronounced impact on the haemolytic activity.^{43,45} Karlotoxins with a longer olefinic side chain exhibit increased potency compared to shorter analogs (KmTx 1, $EC_{50} = 63$ nM, is *ca.* three times more active than KmTx 3, $EC_{50} = 200$ nM). Interestingly, introduction of chlorine has little or no effect on the

haemotoxicity. Similarly to amphidinols, sulfonation of the C1 alcohol leads to a decrease of in activity and might provide an effective avenue for reducing the toxicity of KmTx.

When structural characteristics of KmTx 2 and AM3 are compared, several important findings arise. While both molecules share the absolute configuration in the 1,5-*syn* polyol region (C2, C6, C10) and the relative at C14, the absolute configuration of the *bis*-THP segment is opposite (Figure 3.7.3). Moreover, KmTx 2 features an additional hydroxyl group on one of the THP rings. These modifications in the core of KmTx 2 are remarkable and suggest that karlotoxins are an independent family within amphidinol-like compounds. This could be a subject for further bioactivity studies and provide a better understanding of structure-activity relationships within the linear polyketide family of natural products.

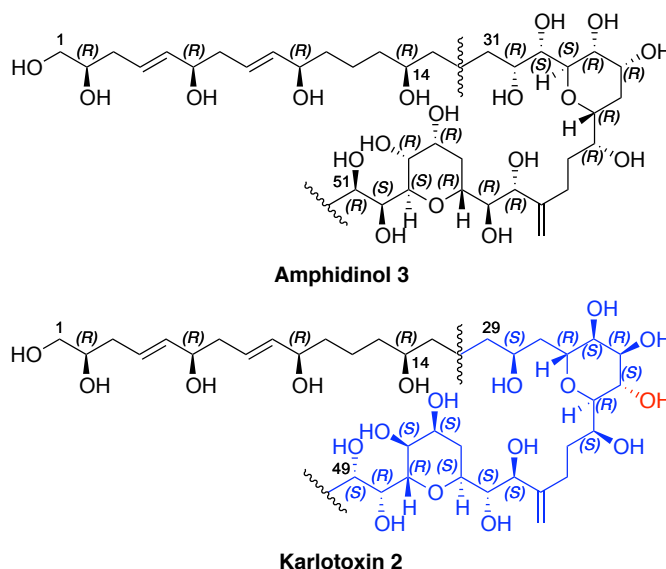


Figure 3.7.3: Main Structural Differences Between AM3 and KmTx 2

Inuzuka, Uemura and co-workers isolated the linear polyol polyketide, amdigenol A, from *Amphidinium sp.* adhered to the surface of marine red alga *Digenea simplex*.⁴⁶ This ‘super-carbon-chain compound’ is the longest polyketide isolated from *Amphidinium sp.* to date. It has a remarkable 98-carbon atom skeleton,

36 secondary hydroxyl groups and three densely substituted THP rings (Figure 3.7.4). The biological evaluation showed weak cytotoxicity against the 3T3-L1 murine adipocyte ($IC_{50} = 59 \mu\text{g/mL}$), but none against HeLa cells. Other biological tests are currently in progress.

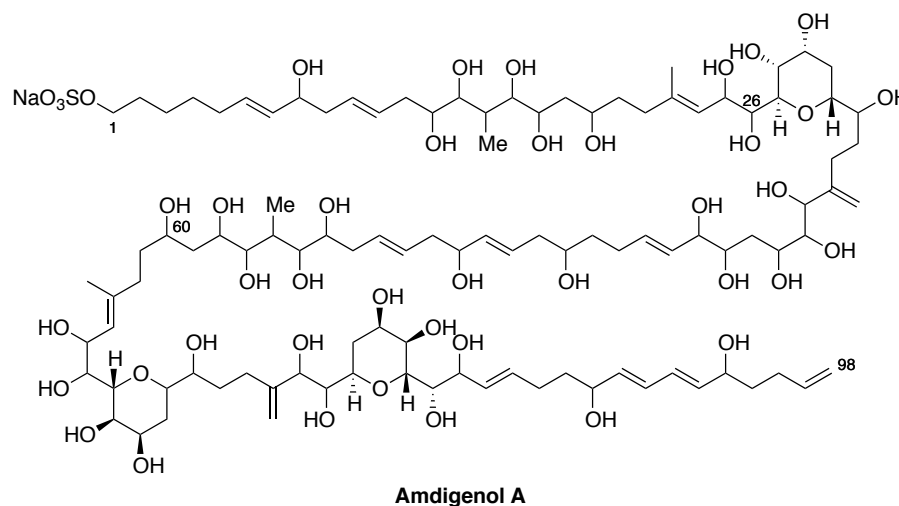


Figure 3.7.4: Structure of Amdigenol A

Uemura *et al.* reported the isolation and structural characterisation of novel antimicrobial polyols, karatungiols, from *Amphidinium sp.*, which is symbiotic with an unknown flatworm, collected at Karatung Island, Indonesia.⁴⁷ These linear polyketides are amphidinol analogs having a unique ketone moiety within the polyol segment of the molecule and terminally saturated alkyl chains, as in karlotoxins (Figure 3.7.5). Karatungiol A has potent antifungal activity against NBRC4407 *A. niger* (12 $\mu\text{g/disc}$) and antiprotozoal activity against *Trichomonas foetus* (1 $\mu\text{g/mL}$).

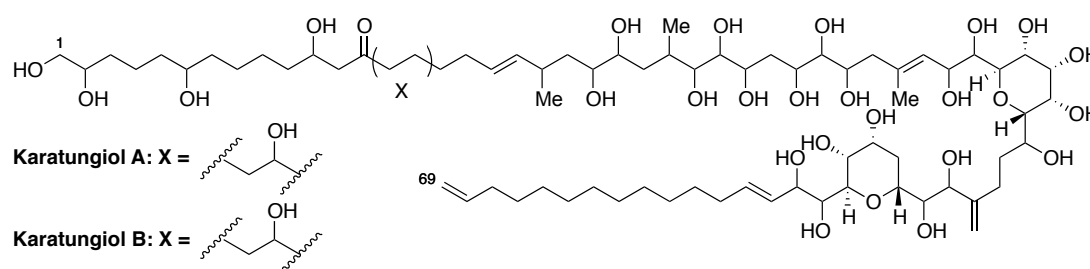


Figure 3.7.5: Structures of Karatungiols A and B

Lingshuiols A and B are other examples of linear polyhydroxyl compounds isolated from the cultured Chinese marine dinoflagellate *Amphidinium sp.*, found in Lingshui Bay, Hainan Province (Figure 3.7.6).⁴⁸ Remarkably, both natural products share the identical hydrophobic polyene system corresponding to amphidinol 2. However, lingshuiol A possesses the same partial C1-C51 structure as luteophanol B, while lingshuiol B has the common C1-C41 part of luteophanol A. Interestingly, the presence of composite structures of luteophanols and amphidinols has little effect on the lingshuiols' biological activity, which has been pronounced as a weak antitumor agent against A-549 and HL-60 cell lines.

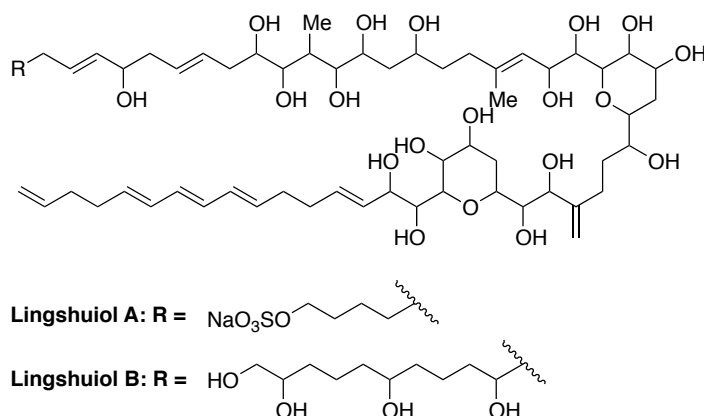


Figure 3.7.6: Structures of Lingshuiols A and B

In 2006, Kobayashi and co-workers isolated an unusual polyhydroxyl metabolite from *Amphidinium sp.* symbiotic with Okinawan marine acoel flatworm *Amphiscolops sp.*⁴⁹ The structure of amphezonol A possesses unique structural elements including a tetrahydrofuran ring in the polyol segment of the molecule, two distantly separated trisubstituted THP rings and an *exo*-methylene group (Figure 3.7.7). These structural features are not common to other metabolites found in *Amphidinium sp.* and are probably responsible for the moderate inhibitory activity of DNA polymerase ($IC_{50} = 15 \mu M$) by this compound.

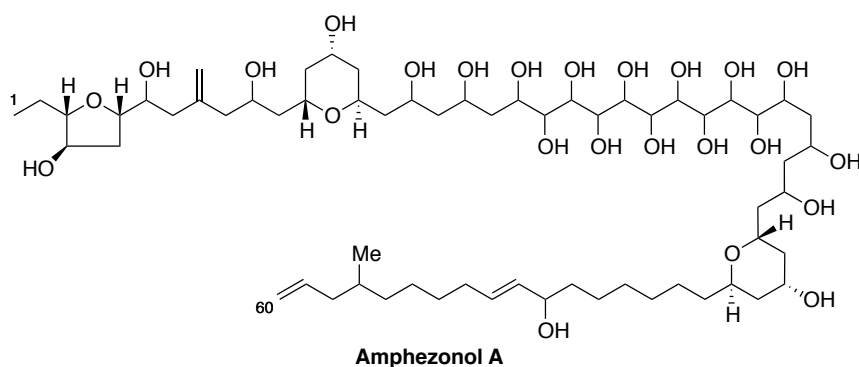


Figure 3.7.7: Structure of *Amphezanol A*

Lu, Huang and others reported the isolation of a potent polyhydroxyl ichthyotoxin from dinoflagellate *Amphidinium carterae*, collected from wash-off epiphytes of the seaweed found on the southern coast of Taiwan.⁵⁰ Carteraol E belongs to the linear polyol polyketide family and has strong similarities to amphidinol 3 in the *bis*-THP and polyene segments (Figure 3.7.8). However, it has a distinctive polyhydroxyl fragment with an uncommon *syn*-THP ring and ketone functionality. Interestingly, carteraol E is the first amphidinol-like derivative that displays potent ichthyotoxic activity ($LD_{50} = 0.28 \mu M$). While this metabolite has strong antifungal action against *A. niger* (15 μg /disk), it shows no cytotoxicity against CCRF-CEM and DLD-1 cancer cells and no antimicrobial activity against the Gram-positive bacterium *Staphylococcus aureus*. This is in a great contrast to the structurally similar lingshuiol and luteophanol A, which are cytotoxic and antimicrobial agents, respectively.

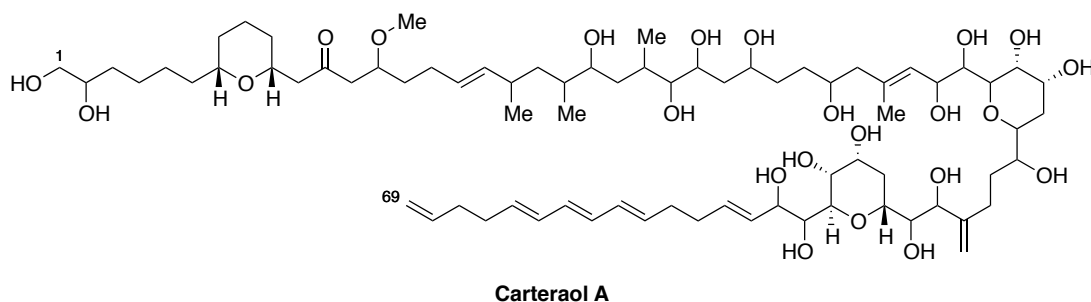


Figure 3.7.8: Structure of *Carteraol E*

Overall, the isolation, biological and structural evaluation of amphidinol-like compounds has provided a powerful insight into the structure-activity relationships of these molecules. This could lead to the development of new types of antibiotic, antifungal and anti-cancer drugs as well as delivering a better understanding of the roles of these polyketides in nature.

3.8 Introduction to the Polyol Fragment of Amphidinol 3

The polyol fragment of amphidinol 3 is a linear C1-C30(31) chain comprised of 10 secondary stereocentres, which includes three repeating 1,5-*syn* diol units, two (*E*)-configured double bonds and a highly functionalised polyacetate/polypropionate-type domain, contoured by a trisubstituted (*E*)-olefin (Figure 3.8.1).

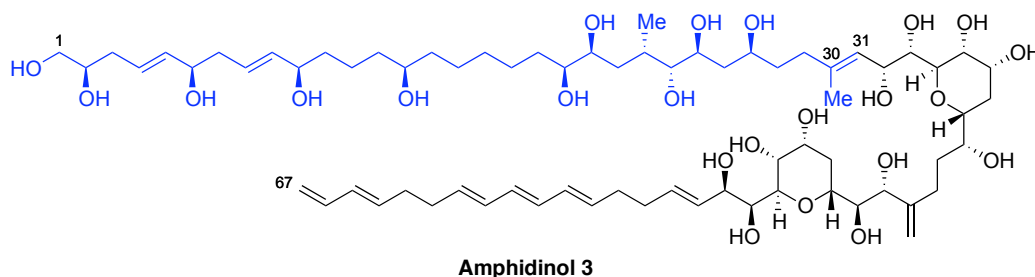


Figure 3.8.1: Polyol Fragment in Amphidinol 3

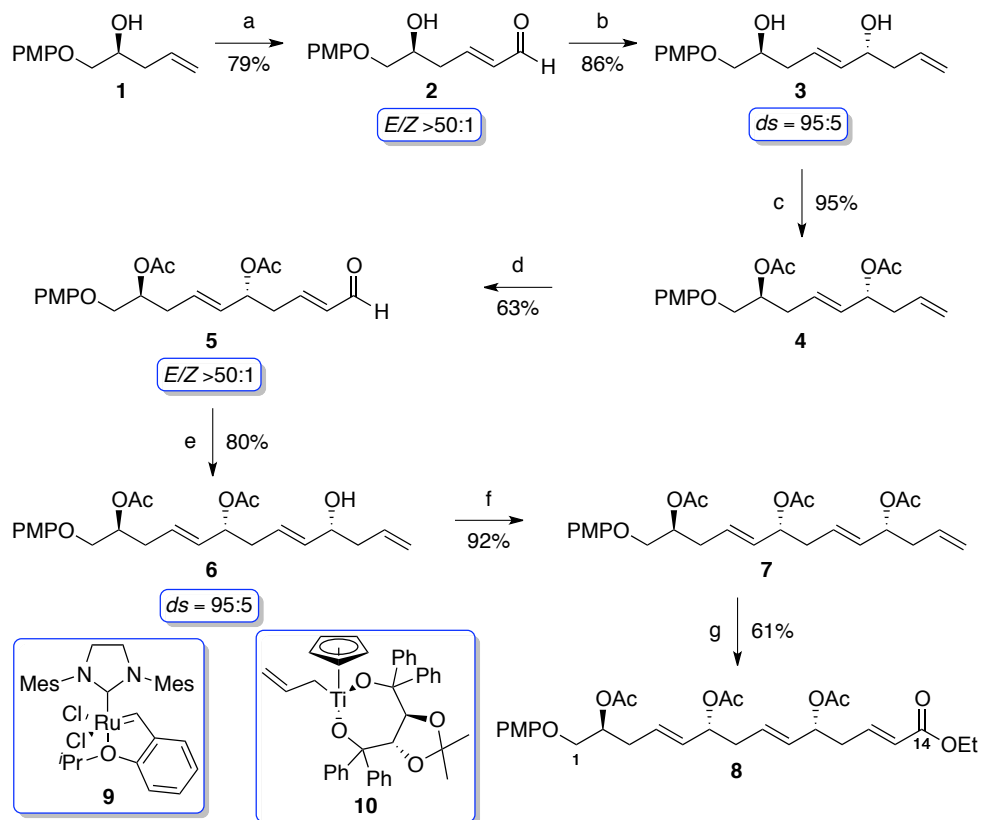
The following sections will overview the synthetic progress made towards the polyol segment of AM3 with particular emphasis on the convergence of each approach and methodologies employed.

3.9 Cossy's Synthesis of the C1-C14 Fragment of Amphidinol 3

In 2001, BouzBouz and Cossy were first to publish synthetic efforts towards the synthesis of AM3.⁵¹ They developed a highly diastereoselective route towards

the C1-C14 polyol fragment based on an iterative chemoselective cross-metathesis/enantioselective allylation sequence (Scheme 3.9.1).

Scheme 3.9.1: *Cossy and BouzBouz Approach Towards the C1-C14 Fragment of Amphidinol 3*



Reaction conditions: a) Acrolein, *cat.* **9**, DCM, RT, $E/Z >50:1$, 79%. b) (*S,S*)-**10**, Et₂O, -78 °C, $ds = 95:5$, 86%. c) Ac₂O, Py, RT, 95%. d) Acrolein, *cat.* **9**, DCM, RT, $E/Z >50:1$, 63%. e) (*S,S*)-**10**, Et₂O, -78 °C, $ds = 95:5$, 80%. f) Ac₂O, Py, RT, 92%. g) Ethyl acrylate, *cat.* **9**, DCM, RT, 61%.

The synthesis commenced by cross-metathesis of the enantiomerically pure homoallylic alcohol **1**⁵² with acrolein, mediated by Hoveyda-Grubbs 2nd generation catalyst **9**,⁵³ to furnish α,β -unsaturated aldehyde **2** with excellent selectivity ($E/Z >50:1$). Enantioselective allyltitanation of **2** using the Hafner and Duthaler complex (*S,S*)-**10**⁵⁴ installed the requisite 1,5-*anti* diol **3** in good yield and exceptional diastereocontrol ($ds = 95:5$). At this point protection of **3** was compulsory to implement the subsequent chemoselective cross-metathesis and avoid

participation of the internal alkene in the catalytic cycle. Thus, formation of diacetate **4** and cross-metathesis of the latter with acrolein using catalytic **9** afforded the α,β -unsaturated aldehyde **5** ($E/Z >50:1$). The observed chemoselectivity was rationalised as a consequence of the deactivation of the allylic acetate double bond due to the electron-withdrawing effect of the acetate group or formation of a non-reactive 6-membered ruthenium chelate.

The succeeding enantioselective allylation of aldehyde **5** with (*S,S*)-**10** gave homoallylic alcohol **6** ($ds = 95:5$) with the strategic formation of the 1,5-*syn* dioxygen functionality. Finally, acetate formation and cross-metathesis with ethyl acrylate installed the last portion of the fragment and furnished α,β -unsaturated ester **8** in acceptable yield and with excellent control of the double bond geometry ($E/Z >50:1$).

In summary, synthesis of the C1-C14 fragment of AM3 was achieved by Cossy and BouzBouz in 7 longest linear steps and 17.5% overall yield. The developed route offered an appealing alternative to a Wittig-Horner reaction/allylation sequence due to the reduced number of protection/deprotection steps and allowed the use of base-sensitive substrates. The highlights include implementation of highly chemoselective cross-metathesis approach in conjunction with asymmetric allyltitanation.

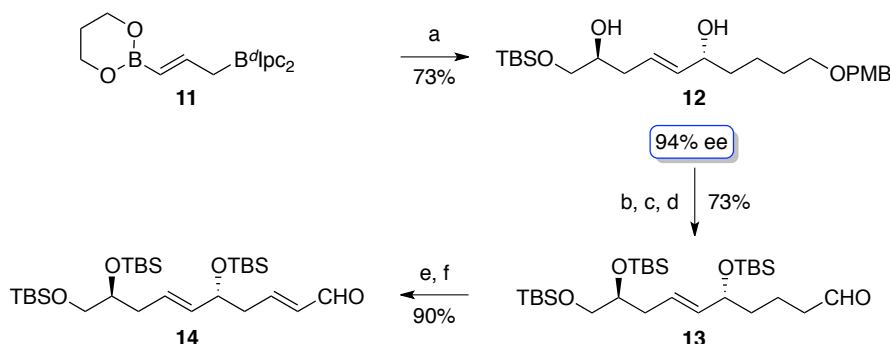
3.10 Roush's Synthesis of the C1-C25 Fragment of Amphidinol 3

In 2005, Roush and Flamme reported an account towards the synthesis of the C1-C25 polyol fragment of AM3.⁵⁵ The remarkable feature of their approach is the application of their earlier developed double allylboration reaction⁵⁶ for the

installation of the 1,5-*syn* and 1,5-*anti* diol units, which proceeded in a highly enantio- and diastereoselective fashion.

The synthesis commenced with a double allylboration reaction of aldehydes **15** and **16** using the *in situ* generated borane **11**⁵⁶ (obtained by reaction of ^dIpc₂BH and 2-allenyl-(1,3,2)-dioxaborinane) (Scheme 3.10.1). Thus, the (*E*)-1,5-*anti* diol **12** was obtained in good yield and with excellent enantioselectivity (94% *ee* by Mosher esters analysis).⁵⁷ Subsequent protection of diol **12** as a *bis*-TBS ether, PMB ether cleavage and Parikh-Doering oxidation⁵⁸ of the resulting primary alcohol afforded aldehyde **13** in 73% overall yield. Enol ether generation from the latter was achieved under mild conditions using *N*-methyl-*N*-(TMS)acetamide and catalytic DBU.⁵⁹ Successive Saegusa–Ito oxidation⁶⁰ furnished the desired (*E*)- α,β -unsaturated aldehyde **14** in excellent overall yield (90%).

Scheme 3.10.1: *Synthesis of Aldehyde 14 via Double Allylboration*

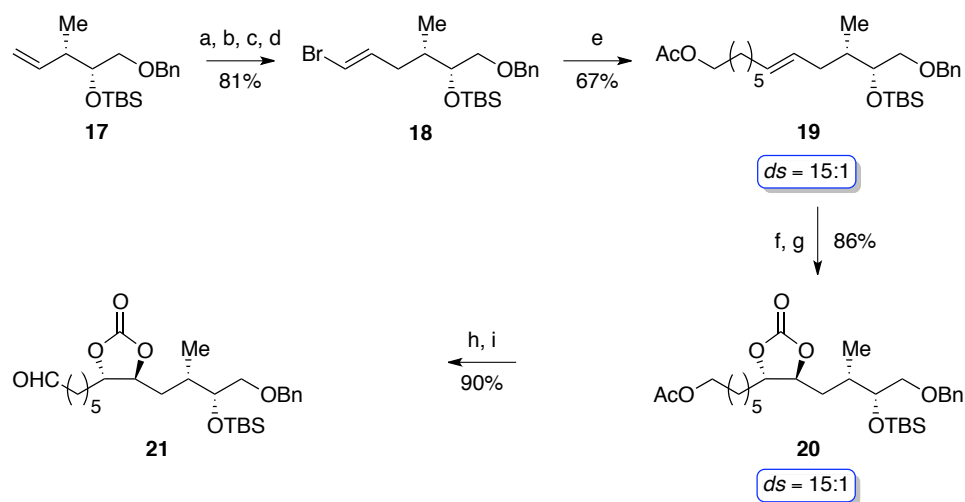


Reaction conditions: a) i. PMBO(CH₂)₄CHO (**15**), Et₂O, -78 °C to RT. ii. TBSOCH₂CHO (**16**), Et₂O, -78 °C. iii. NaOH/H₂O₂, 0 °C, 94% *ee*, 73%. b) TBSCl, imid, *cat.* DMAP, DMF/DCM (1:1), 0 °C. c) DDQ, DCM/pH 7 buffer (13:1), 0 °C. d) SO₃·Py, DIPEA, DMSO, DCM, 0 °C, 73% over 3 steps. e) MSA, DBU, DMF, (*E/Z* = 4:1), 40 °C. f) Pd(OAc)₂, MeCN/DMF (4:1), RT, 90% over 2 steps.

The synthesis of the advanced aldehyde **21** is depicted in Scheme 3.10.2. Hydroboration/oxidation of the known TBS protected homoallylic alcohol **17**⁶¹ with 9-BBN followed by Parikh-Doering⁵⁸ oxidation of resultant primary alcohol gave an intermediate aldehyde. Gilbert-Seyferth homologation⁶² of the latter aldehyde,

followed by hydrozirconation/bromination⁶³ delivered vinyl bromide **18** in 75% yield over four steps. The *B*-alkyl Suzuki coupling⁶⁴ of the alkylboronate generated from alkene **22** and 9-BBN afforded (*E*)-olefin **19** (*ds* = 15:1), along with inseparable 1,1-disubstituted double bond addition product with good selectivity. Sharpless asymmetric dihydroxylation⁶⁵ with AD-mix- α (*ds* = 15:1) and subsequent diol protection as a cyclic carbonate allowed easy separation of isomers. Finally, mild acetate group deprotection using a mixture of guanidine and guanidinium nitrate in methanol,⁶⁶ followed by Dess-Martin oxidation⁶⁷ furnished aldehyde **21**.

Scheme 3.10.2: Elaboration of Aldehyde 21

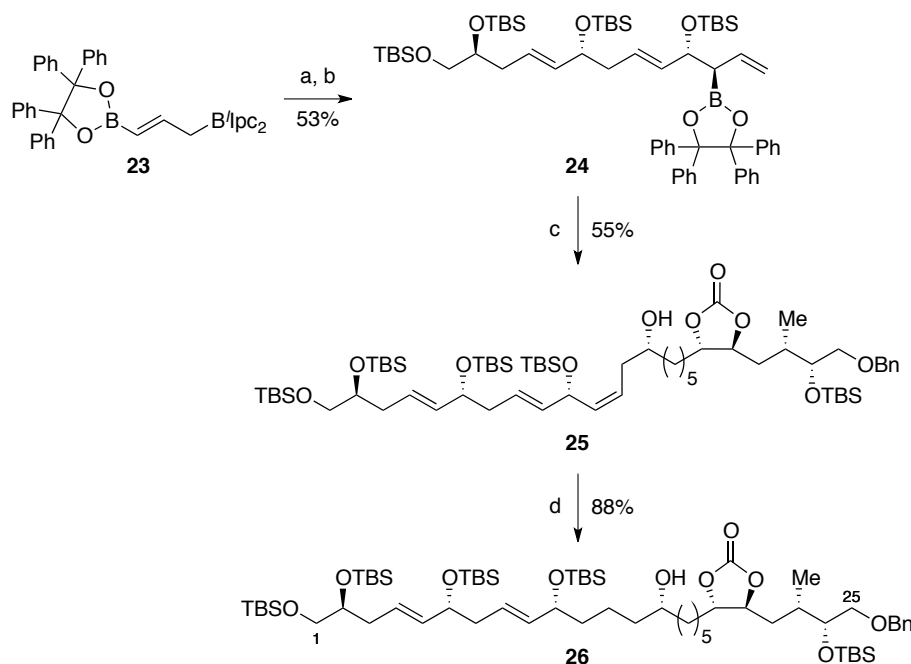


Reaction conditions: a) 9-BBN, 0 °C to RT, THF, then NaOH/H₂O₂, 0 °C to RT, 99%. b) SO₃·Py, DIPEA, DMSO, DCM, 0 °C, 94%. c) (MeO)₂P(O)CHN₂, KO^tBu, THF, -78 °C to RT, 88%. d) Cp₂Zr(H)Cl, NBS, DCM, RT, 99%. e) i. AcO(CH₂)₄CHCH₂ (**22**), 9-BBN, THF, 0 °C to RT. ii. **18**, K₃PO₄·H₂O, Pd(dppf)·DCM, DMF/H₂O (1:1), *ds* = 15:1, 67%. f) AD-mix- α , ^tBuOH/H₂O (1:1), 0 °C, *ds* = 15:1, 93%. g) (CCl₃O)₂CO, Py, DCM, -78 °C to -30 °C, 93%. h) Guanidinium nitrate, NaOMe, MeOH/DCM (9:1), RT, 95%. i) DMP, Py, DCM, 0 °C, 95%.

To complete the synthesis of the fragment authors exploited an interrupted double allylboration sequence (Scheme 3.10.3). Reaction of the *in situ* generated boronate **23**⁵⁶ (*vide supra*) with the advanced aldehyde **14**, followed by methanol quench and TBS protection of the resultant alcohol afforded the labile allylboronate intermediate **24** in 53% yield and with good stereocontrol (*ds* = 10:1). It is

noteworthy that the interruption of the allylboration was required in order to chemically distinguish the 1,5-diol that was generated in the double allylation sequence. Boronate **24** was then reacted with the second advanced aldehyde, **21**, which resulted in the (*Z*)-homoallylic alcohol **25**. By taking advantage of free homoallylic alcohol in **25**, a hydroxyl-directed hydrogenation⁶⁸ was employed to reduce the C8-C9 (*Z*)-alkene. After extensive optimisation it was found that Noyori's catalyst, (*S*)-Ru(BINAP)(OAc)₂,⁶⁹ facilitated the selective olefin hydrogenation and furnished the C1-C25 fragment of AM3 in 88% yield.

Scheme 3.10.3: Completion of the C1-C25 Fragment of Amphidinol 3



Reaction conditions: a) **14**, DCM, -78°C , then MeOH, RT, *ds* = 10:1, 63%. b) TBSOTf, 2,6-lutidine, DCM, -78°C to -10°C , 85%. c) **21**, DCM, -78°C to RT, then MeOH, RT, 55%. d) H₂ (1500 psi), *cat.* (*S*)-Ru(BINAP)(OAc)₂, DCM/MeOH (2:1), RT, 88%.

In conclusion, Roush and Flamme developed an asymmetric synthesis of the C1-C25 polyol fragment of AM3 in 11 linear steps and 19% overall yield. The salient feature of the synthesis includes the application of double allylboration methodology to stereoselectively access 1,5-*syn/anti* diols in conjunction with the

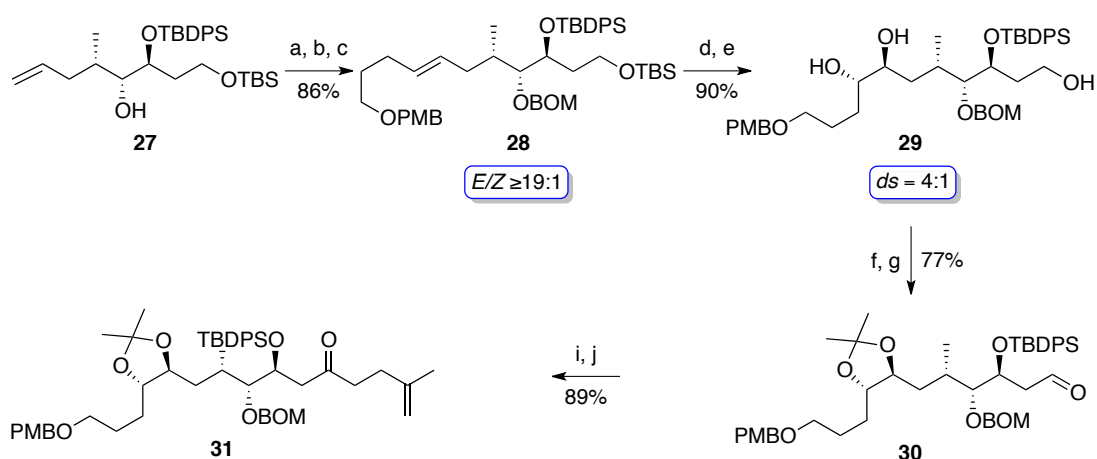
strategic coupling of fragments. Notably, the ability to perform the interrupted double allylboration reaction allowed chemical differentiation of the alcohols formed. The latter feature was used to execute a chemoselective hydroxyl-directed olefin reduction.

3.11 Paquette's Synthesis of the C1-C30 Fragment of Amphidinol 3

In 2005, Paquette and Chang reported a route to the C1-C30 fragment of amphidinol 3.⁷⁰ In their approach, the Kocienski-modified Julia olefination⁷¹ was used as a key coupling reaction for the elaboration of the polyol skeleton.

The synthesis was initiated with the homologation of alcohol **27** (Scheme 3.11.1). BOM protection of the secondary alcohol, followed by ozonolysis and Julia-Kocienski olefination⁷¹ with potassium salt of sulfone **32**, afforded olefin **28** as single geometrical isomer ($E/Z \geq 19:1$). Chemoselective primary TBS ether deprotection, succeeded by Sharpless asymmetric dihydroxylation⁶⁵ furnished triol **29** with moderate selectivity ($ds = 4:1$), favouring the required diastereoisomer.

Scheme 3.11.1: Synthesis of the Ketone Intermediate **31**

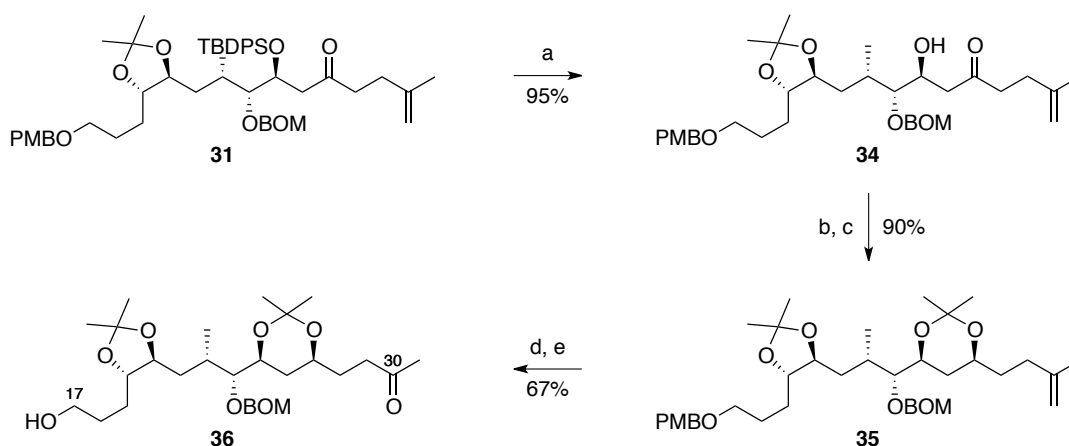


Reaction conditions: a) BOMCl, DIPEA, *cat.* TBAI, RT, 98%. b) O₃, DCM, -78 °C, then PPh₃, -78 °C to RT, 96%. c) PMBO(CH₂)₄SO₂PT (**32**), KHMDS, THF, -78 °C to RT, $E/Z \geq 19:1$, 91%. d) CSA, MeOH/H₂O (1:1), 0 °C, 95%. e) AD-mix- α , ^tBuOH/H₂O (1:1), 0 °C, $ds = 4:1$, 95%. f) 2,2-DMP, *cat.* PPTS, RT, 85%. g) DMP, Py, DCM, 0 °C to RT, 91%. i) 4-Bromo-2-methyl-1-butene (**33**), Mg, -78 °C to -40 °C, THF, 90%. j) DMP, Py, DCM, 0 °C to RT, 90%.

The order of steps in the latter sequence proved to be crucial for the efficient separation of dihydroxylation stereoisomers. The advanced aldehyde **30** was obtained through acetonide formation and primary alcohol oxidation using Dess-Martin periodinane⁶⁷ buffered with pyridine (71% yield). Subsequent installation of the 2-methyl-1-butene fragment was not trivial since the lithium-based reagent, generated from 4-bromo-2-methyl-1-butene **33**, induced β -elimination in aldehyde **30**. However, addition of a Grignard reagent, derived from **33**, proceeded readily and afforded **31** after oxidation of the intermediate alcohol (89% over 2 steps).

The base sensitivity persisted in **31**, thus TBAF buffered with acetic acid was required to efficiently remove the secondary TBDPS ether (Scheme 3.11.2).⁷² The resultant β -hydroxy ketone **34** was submitted to diastereoselective 1,3-*syn* reduction with diethylmethoxyborane,⁷³ followed by the acetonide formation to furnish **35** in 90% overall yield.

Scheme 3.11.2: Completion of the C17-C30 Fragment of AM3

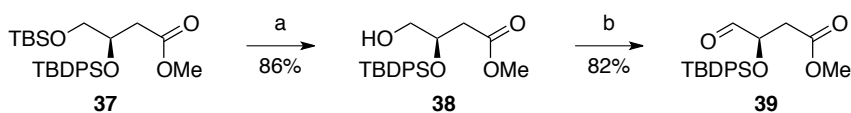


Reaction conditions: a) TBAF, AcOH/H₂O (2:1), 50 °C, 95%. b) Et₂BOMe, NaBH₄, THF/MeOH (3:1), -78 °C to RT, 94%. c) 2,2-DMP, *cat.* PPTS, RT, 96%. d) DDQ, DCM/H₂O (5:1), 0 °C, 86%. e) *cat.* OsO₄, NaIO₄, THF/aq. KH₂PO₄, K₂HPO₄ buff. (1:1), RT, 78%.

The synthesis of the C17-C30 fragment **36** was secured by primary PMB ether deprotection using DDQ and Johnson-Lemieux oxidative cleavage of the *exo*-olefin.⁷⁴

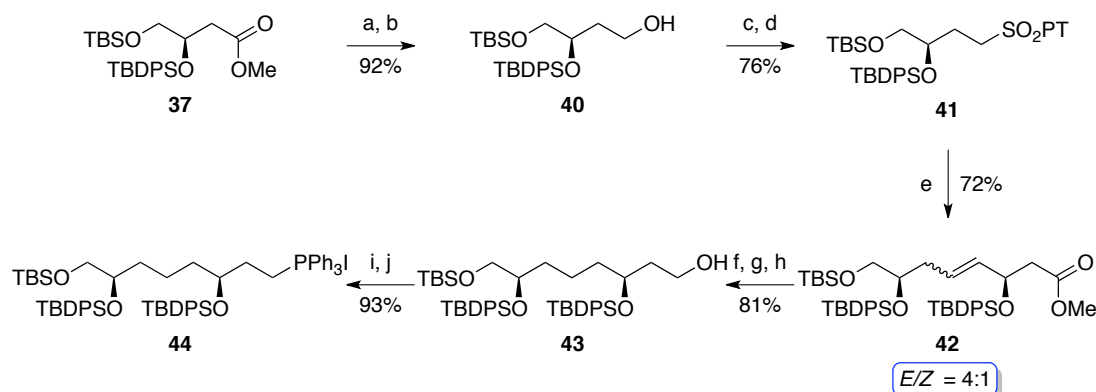
The differentially protected intermediate **39** derived from *D*-malic acid was used as a common fragment for the construction of compounds **44** and **54** (Scheme 3.11.3). Carefully controlled primary TBS ether removal was achieved with CSA in a mixture of DCM and MeOH at $-10\text{ }^{\circ}\text{C}$ in order to avoid the competitive lactonisation. Successive oxidation with buffered Dess-Martin periodinane⁶⁷ furnished aldehyde **39**.

Scheme 3.11.3: Synthesis of Aldehyde 39



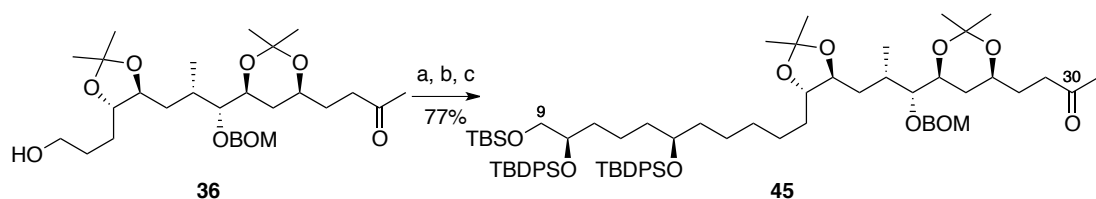
Reaction conditions: a) CSA, MeOH/DCM (1:1), $-10\text{ }^{\circ}\text{C}$, 86%. b) DMP, Py, DCM, $0\text{ }^{\circ}\text{C}$ to RT, 82%.

Elaboration to phosphonium salt **44** commenced with a two-step reduction of ester **37** to the corresponding alcohol **40** (Scheme 3.11.4). Lactone formation appeared to be the main competitive reaction, thus the temperature control proved to be critical for obtaining **40** in high yield. The latter was converted to sulfone **41**, ready for Julia-Kocienski olefination,⁷¹ *via* Mitsunobu reaction with PTSH,⁷⁵ followed by oxidation with H_2O_2 .⁷⁶ Condensation of sulfone **41** with aldehyde **39** proceeded with moderate stereocontrol ($E/Z = 4:1$), which was of no consequence since the resulting olefin **42** was catalytically hydrogenated and the ester reduced to alcohol **43** in 81% overall yield. Finally, conversion to phosphonium iodide **44** was achieved in excellent yield *via* the intermediacy of the primary iodide.

Scheme 3.11.4: Synthesis of the Phosphonium Salt 44

Reaction conditions: a) DIBAL-H, DCM, $-78\text{ }^{\circ}\text{C}$. b) NaBH_4 , THF/MeOH (2:1), $0\text{ }^{\circ}\text{C}$, 92% over 2 steps. c) PTSH, DIAD, PPh_3 , THF, $0\text{ }^{\circ}\text{C}$. d) $\text{Mo}_7\text{O}_{24}(\text{NH}_4)_6$, H_2O_2 , EtOH, $0\text{ }^{\circ}\text{C}$ to RT, 76% over 2 steps. e) **37**, KHMDS, THF, $-78\text{ }^{\circ}\text{C}$ to RT, $E/Z = 4:1$, 72%. f) H_2 , *cat.* 10% Pd/C, RT, EtOAc, 91%. g) DIBAL-H, DCM, $-78\text{ }^{\circ}\text{C}$. h) NaBH_4 , THF/MeOH (2:1), $0\text{ }^{\circ}\text{C}$, 89% over 2 steps. i) I_2 , PPh_3 , imid, THF, $0\text{ }^{\circ}\text{C}$, quant. j) PPh_3 , DIPEA, MeCN, $85\text{ }^{\circ}\text{C}$, 93%.

The Wittig reagent **44** was used in the elaboration to the C9-C30 fragment of AM3 (Scheme 3.11.5). Oxidation of the primary alcohol **36** to the corresponding aldehyde, followed by Wittig olefination with the phosphonium salt **44** afforded the (*Z*)-olefin (^1H NMR), which was successively hydrogenated using Pd/C to afford the polyhydroxy segment **45** in high overall yield.

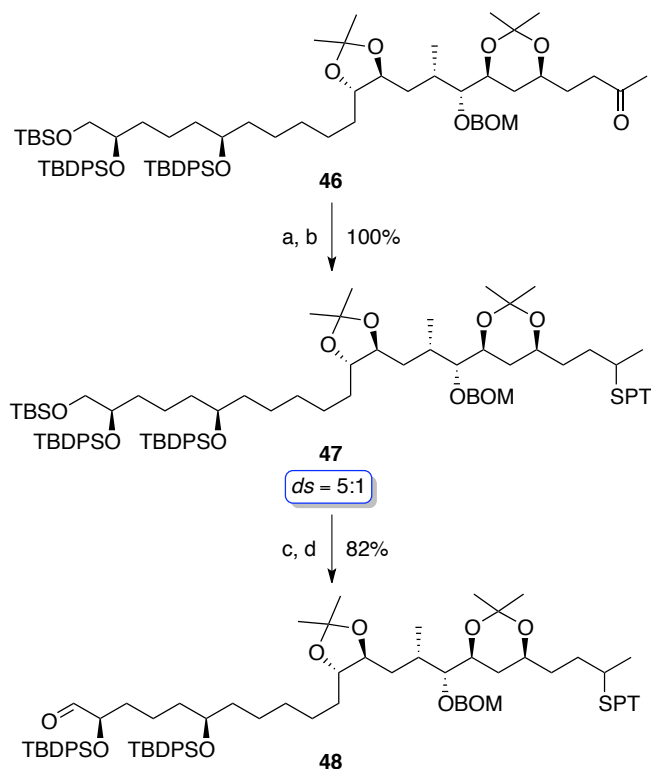
Scheme 3.11.5: Elaboration of Ketone 45

Reaction conditions: a) DMP, Py, DCM, $0\text{ }^{\circ}\text{C}$ to RT, quant. b) **44**, $\text{MeLi}\cdot\text{LiBr}$, THF, $-78\text{ }^{\circ}\text{C}$ to RT, 77%. c) H_2 (60 psi.), *cat.* 10% Pd/C, EtOAc, quant.

Further reduction of ketone **45** with NaBH_4 in MeOH/THF mixture and Mitsunobu reaction⁷⁵ of the resulting alcohol with PTSH gave sulfide **47** as a mixture of separable diastereoisomers ($ds = 5:1$) (Scheme 3.11.6). Although, each of them could be ultimately converted into the same alkene product, chromatographic

separation was undertaken and individual isomers were independently examined in the subsequent reactions. Chemoselective deprotection of the primary TBS ether in the presence of TBDPS was achieved using NBS in aqueous DMSO,⁷⁷ and was followed by oxidation to furnish aldehyde **48** ready for olefination.

Scheme 3.11.6: Completion of the C9-C30 Fragment of Amphidinol 3

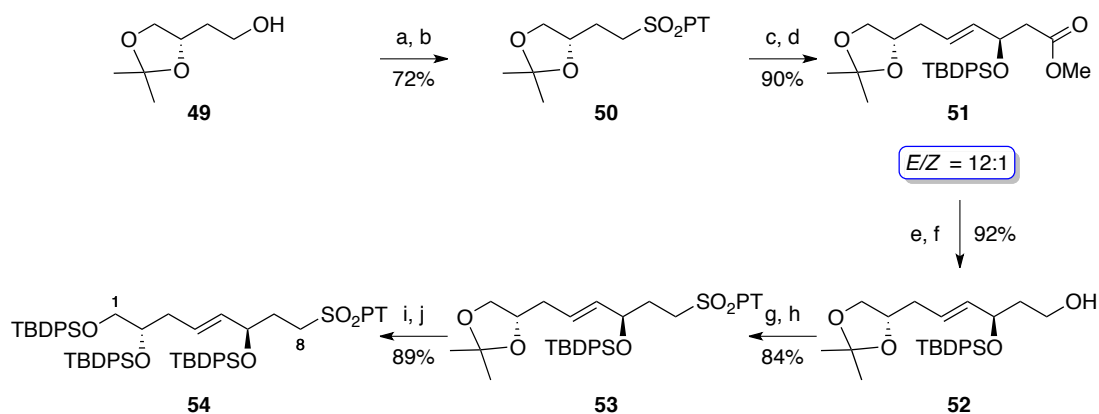


Reaction conditions: a) NaBH₄, THF/MeOH (2:1), 0 °C. b) PTSH, DIAD, PPh₃, THF, 0 °C to RT, $ds = 5:1$, quant. over 2 steps. c) NBS, aq. DMSO/THF (2:1), 0 °C to RT, 86% (b.r.s.m.). d) DMP, Py, DCM, 0 °C to RT, 95%.

Further efforts were directed towards the synthesis of sulfone **54** and its strategic coupling with the advanced aldehyde **48** (Scheme 3.11.7). The synthesis of the C1-C8 sulfone **54** proceeded from the known alcohol **49**, which could be obtained from dimethyl (*S*)-malate in two steps.⁷⁸ Mitsunobu reaction of **49** with PTSH,⁷⁵ followed by molybdate-catalysed oxidation resulted in sulfone **50**.⁷⁶ Julia-Kocienski coupling⁷¹ of the latter with the common intermediate **39** gave a 3:1 mixture of *E/Z* isomers of **51**, which gratifyingly could be enriched to 12:1 *via*

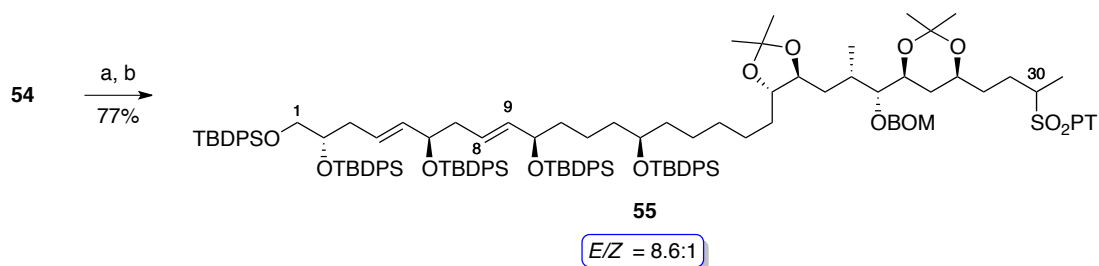
radical-induced isomerisation using AIBN and thiophenol in excellent overall yield.⁷⁹ Although the separation of isomers was inconceivable at this stage, the sulfone **54** was isolated after chromatography as a single geometrical isomer. Towards this end, the ester functionality in **51** was reduced to alcohol **52** and this was converted into sulfone **53** using standard Mitsunobu/oxidation route (*vide supra*). Finally, acetonide group replacement with two TBDPS groups afforded **54** ready for the final Julia-Kocienski coupling.⁷¹

Scheme 3.11.7: Synthesis of the C1-C8 Sulfone Fragment 54



Reaction conditions: a) PTSH, DIAD, PPh₃, 0 °C to RT, THF, 86%. b) Mo₇O₂₄(NH₄)₆, H₂O₂, EtOH, RT, 84%. c) **39**, KHMDS, THF, -78 °C to RT, *E/Z* = 3:1, 90%. d) PhSH, AIBN, benzene, reflux, *E/Z* = 12:1, quant. e) DIBAL-H, -78 °C, DCM. f) NaBH₄, THF/MeOH (2:1), 0 °C, 92% over 2 steps. g) PTSH, DIAD, PPh₃, THF, 0 °C to RT, 96%. h) Mo₇O₂₄(NH₄)₆, H₂O₂, EtOH, 0 °C to RT, 88%. i) CuCl₂·2H₂O, MeOH, reflux. j) TBDPSCl, DMAP, imid, DMF, 50 °C, 89% over 2 steps.

The formation of the C8-C9 olefin in fragment **55** was then secured *via* the reaction of potassium salt of **54** with aldehyde **48** at -78 °C in THF (Scheme 3.11.8). The coupling provided the strategic union of the two polyol fragments in excellent yield and with good stereocontrol (*E/Z* = 8.6:1). Subsequent sulfide oxidation with ammonium molybdate hydrogen peroxide complex⁷⁶ furnished the fully protected C1-C30 fragment of amphidinol 3.

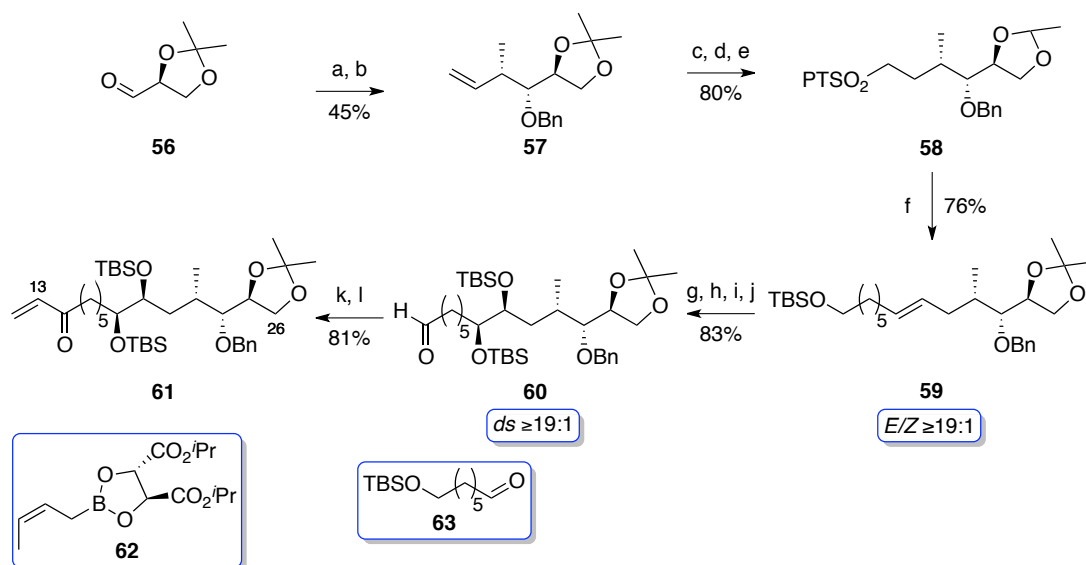
Scheme 3.11.8: Completion of the C1-C30 Fragment of Amphidinol 3

Reaction conditions: a) **48**, KHMDS, THF, -78°C to RT, $E/Z = 8.6:1$, 81%. b) $\text{Mo}_7\text{O}_{24}(\text{NH}_4)_6$, H_2O_2 , EtOH/acetone (1:1), RT, 95%.

In summary, Paquette and Chang developed a highly convergent route to the C1-C30 fragment of amphidinol 3, which was achieved in 24 longest linear steps and 13.5% overall yield. The key features include the application of consecutive Julia-Kocienski olefinations as the crucial olefin formation reaction and the utilisation of antipodal malic acids for the synthesis of the polyol building blocks.

3.12 Rychnovsky's Synthesis of the C1-C26 Fragment of Amphidinol 3

In 2007, Rychnovsky *et al.* reported the synthesis of the C1-C26 fragment of amphidinol 3.⁸⁰ The synthesis of the C13-C26 fragment is depicted in Scheme 3.12.1. The known (*S*)-glyceraldehyde acetonide **56** underwent *syn*-crotylation using Roush's protocol,⁸¹ followed by benzyl protection of the resulting secondary alcohol, which proceeded in moderate overall yield. Subsequent hydroboration/oxidation, sulfide formation and oxidation of the latter with H_2O_2 ⁷⁶ furnished the Julia-Kocienski coupling partner **58** in 80% overall yield. Coupling of **58** with the known aldehyde **63** proceeded with good yield and afforded **59** as a single (*E*)-isomer. Sharpless asymmetric dihydroxylation⁶⁵ of the newly formed olefin gave diol with excellent diastereocontrol ($ds \geq 19:1$).

Scheme 3.12.1: Synthesis of the C13-C26 Enone **61**

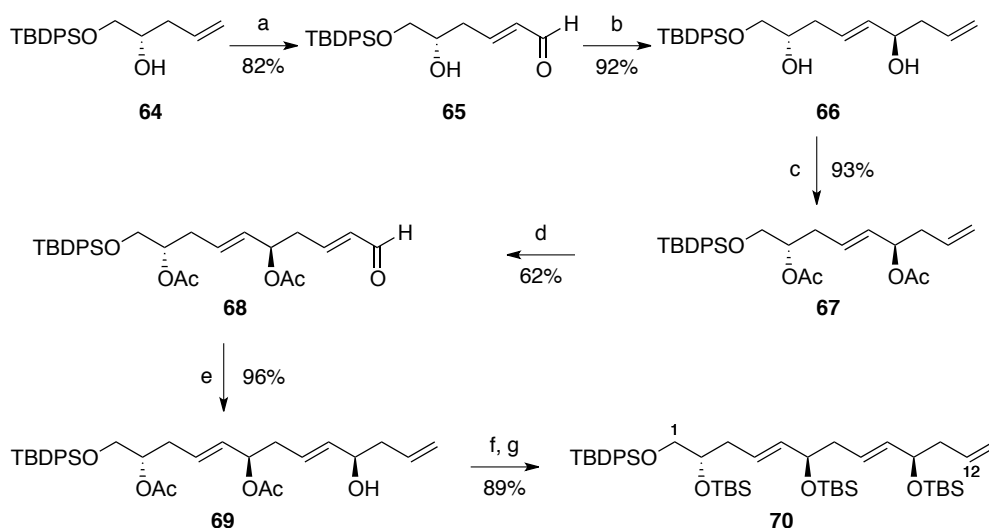
Reaction conditions: a) **62**, 4 Å MS, PhMe, -78°C , 50%. b) NaH, BnBr, TBAI, THF, 60°C , 95%. c) i. 9-BBN, THF, 0°C to RT. ii. NaOH, H_2O_2 , 50°C , 91%. d) PTSH, DIAD, PPh_3 , THF, 0°C to RT, 94%. e) $\text{Mo}_7\text{O}_{24}(\text{NH}_4)_6$, H_2O_2 , EtOH, 0°C to RT, 93%. f) **63**, KHMDS, DME, -56°C to RT, $E/Z \geq 19:1$, 76%. g) AD-mix- α , $t\text{BuOH}/\text{H}_2\text{O}$ (1:1), 0°C , $ds \geq 19:1$, 98%. h) TBSOTf, 2,6-lutidine, DCM, 0°C , 98%. i) Al_2O_3 , hexanes, RT, 95%. j) IBX, THF/DMSO (1:1), RT, 91%. k) VinylMgBr, THF, -78°C , 93%. l) IBX, THF/DMSO (1:2), RT, 87%.

Bis-silylation of the secondary diols with TBS chloride, chemoselective deprotection of the primary TBS ether and IBX mediated oxidation⁸² of the resultant primary alcohol afforded aldehyde **60** in excellent 83% yield over 4 steps. The formation of enone **61** was accomplished by vinylmagnesium bromide addition to aldehyde **60** and oxidation of the resulting allylic alcohol.

The next challenge was the coupling of two polyol segments **61** and **70**. Initially, the authors envisaged addition of an organozinc reagent,⁸³ derived from **70**, to aldehyde **60**. However, formation of the organozincate proved to be elusive and they turned their attention to the coupling using cross-metathesis reaction.⁸⁴ Towards this end, the alkene coupling partner **70** was prepared using the modified Cossy's metathesis route⁵¹ (*vide supra*) (Scheme 3.12.2). The main difference from the original route is the elaboration of the final fragment **69** as an all-silyl ether, which is consistent with the overall plan of final global deprotection by desilylation.

The synthesis of **70** begun from the known allylic alcohol **64**,⁸⁵ which could be accessed from (*R*)-glycidol in 2 steps. Cross-metathesis with acrolein mediated by Hoveyda-Grubbs 2nd generation catalyst⁵³ gave enal **65**. Hafner-Duthaler allyltitanation⁵⁴ of the latter followed by protection of the resulting diol as diacetate produced **67** in excellent overall yield. A second cross-metathesis with acrolein and allylation gave **69**, which was submitted to reductive deacetylation using DIBAL-H. Finally, TBS protection of the triol afforded the alkene fragment **70** ready for the crucial coupling of the two polyol fragments.

Scheme 3.12.2: Synthesis of the C1-C12 Alkene 70



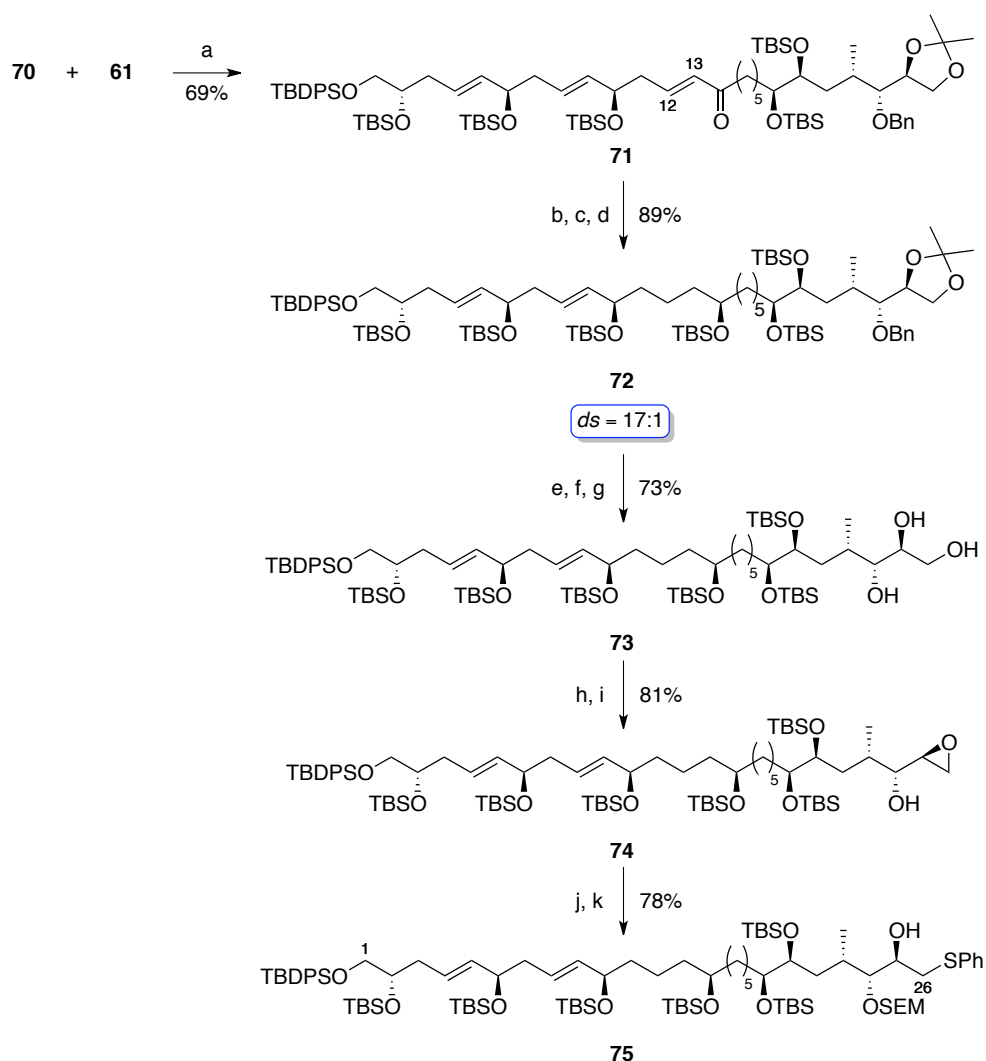
Reaction conditions: a) Acrolein, *cat.* **9**, RT, DCM, 82% b) (*S,S*)-**10**, Et₂O, -78 °C, 92%. c) Ac₂O, Py, RT, 93%. d) Acrolein, *cat.* **9**, RT, DCM, 62%. e) (*S,S*)-**10**, Et₂O, -78 °C, 96%. f) DIBAL-H, DCM, -78 °C, 98%. g) TBSOTf, 2,6-lutidine, DCM, 0 °C, 91%.

The highly effective union of fragments **70** and **61** was achieved *via* cross-metathesis using an equimolar ratio of both reactants mediated by Hoveyda-Grubbs 2nd generation catalyst⁵³ in 69% yield (Scheme 3.12.3). CBS reduction⁸⁶ was applied for the stereoselective enone **71** reduction (*ds* = 17:1). Then, in accordance to Roush's precedent,⁵⁵ the chemoselective hydroxyl-directed C12-C13 alkene

reduction was carried out using Noyori's catalyst.⁶⁹ The resulting alcohol was then protected to deliver **72** in excellent 89% overall yield.

The next synthetic operations were directed towards the synthesis of the phenyl sulfide **75**, which could be used in a β -alkoxy alkyl lithium coupling reaction.⁸⁷ For this purpose 1,2-acetonide deprotection, proceeding through the enol ether formation, and hydrolysis⁸⁸ was carried out.

Scheme 3.12.3: Completion of the C1-C26 Fragment of Amphidinol 3



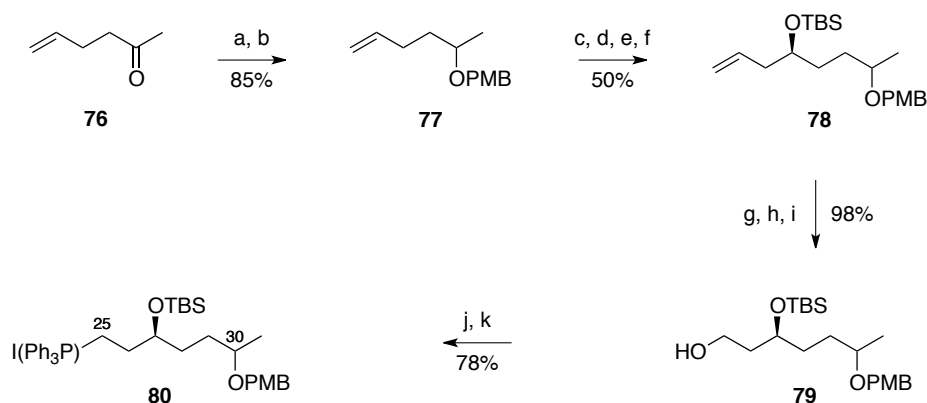
Reaction conditions: a) *cat.* HG-II, DCM, RT, 69%. b) (*S*)-CBS, DCM, $-78\text{ }^{\circ}\text{C}$, *ds* = 17:1, 92%. c) H_2 (1,500 psi), (*S*)-Ru(BINAP)(OAc)₂, DCM/MeOH (2:1), 97%. d) TBSOTf, 2,6-lutidine, DCM, $0\text{ }^{\circ}\text{C}$, 100%. e) i. TMSOTf, DIPEA, $0\text{ }^{\circ}\text{C}$ to RT. ii. aq. NaHSO_4 , RT. f) Citric acid, MeOH/DCM (3:1), RT, 87% over 2 steps. g) LiDBB, THF, $-78\text{ }^{\circ}\text{C}$, 84%. h) MsCl, collidine, DCM, $0\text{ }^{\circ}\text{C}$ to $7\text{ }^{\circ}\text{C}$, 86%. i) K_2CO_3 , MeOH/DCM (3:1), RT, 94%. j) SEMCl, DIPEA, DCM, $0\text{ }^{\circ}\text{C}$ to $40\text{ }^{\circ}\text{C}$, 15 h, 93%. k) PhSH, NaH, THF, $0\text{ }^{\circ}\text{C}$ to $50\text{ }^{\circ}\text{C}$, 84%.

Subsequent single-electron reductive removal of the secondary benzyl group gave triol **73** in 73% yield over 3 steps. Formation of hydroxy epoxide **74** was achieved *via* the intermediacy of the primary mesylate and subsequent K₂CO₃ mediated *intramolecular* cyclisation. Finally, SEM protection of **74**, followed by sodium thiophenolate addition to the epoxide furnished the phenylsulfide **75** and constituted the C1-C26 fragment of AM3.

The route described by Rychnovsky and co-workers allowed for convergent and efficient preparation of the C1-C26 segment of amphidinol 3 with a longest linear sequence of 23 steps and in 5.5% overall yield. The key features of the synthesis are the stereoselective metathesis coupling of two major olefinic fragments to access the polyol subunit and hydroxyl-directed allylic alkene reduction using Noyori's catalyst. Other highlights include the construction of the 1,5-*syn/anti* polyol fragments employing methodology developed by Cossy and the synthesis of the second alkene fragment using Roush crotylboration and Julia-Kocienski olefination.

3.13 Cossy's and Marko's Synthesis of the C18-C30 Fragment of Amphidinol 3

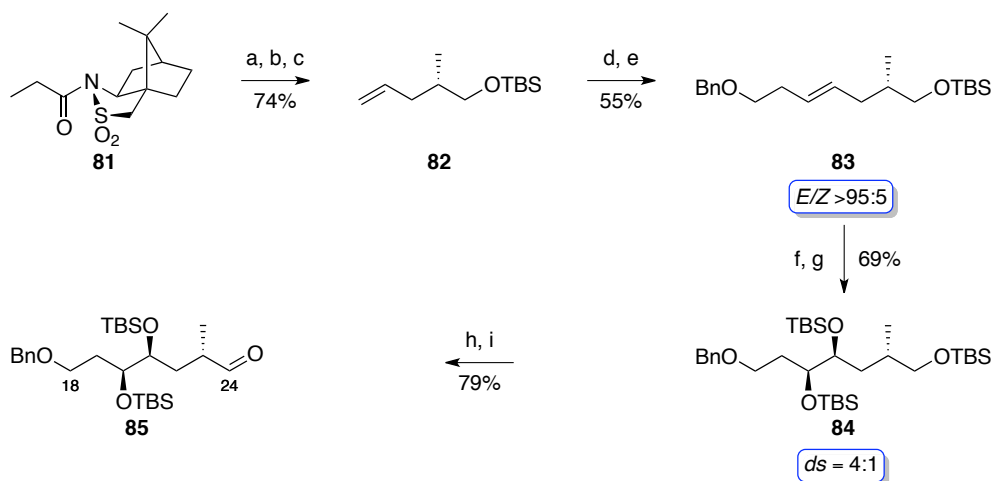
In 2009, Cossy, Marko and co-workers published their route to the C18-C30 fragment of amphidinol 3, which possesses 6 of the 25 stereogenic centres present in the molecule.⁸⁹ The realisation of their approach is depicted in Scheme 3.13.1. The PMB ether **77** was prepared from γ,δ -unsaturated ketone **76** using NaBH₄ reduction and protection of the secondary alcohol with PMB-imidate under mildly acidic conditions. The resultant racemic unsaturated ether was submitted to the oxidative cleavage of the olefin,⁷⁴ followed by asymmetric allylation using complex (*S,S*)-**10**⁵⁴ and TBS protection to give **78** in 50% yield over 4 steps.

Scheme 3.13.1: Synthesis of the Phosphonium Salt **80**

Reaction conditions: a) NaBH_4 , MeOH, Et_2O , RT. b) $\text{PMBOC}(\text{CCl}_3)\text{NH}$, CSA, $\text{C}_6\text{H}_{12}/\text{DCM}$, 85% over 2 steps. c) *cat.* OsO_4 , NMO, $t\text{BuOH}/\text{H}_2\text{O}$, RT. d) NaIO_4 , THF/ H_2O . e) (*S,S*)-**10**, Et_2O , -78° . f) TBSOTf , 2,6-lutidine, DCM, -78°C to RT, 50% over 4 steps. g) *cat.* OsO_4 , NMO, $t\text{BuOH}/\text{H}_2\text{O}$, RT. h) NaIO_4 , THF/ H_2O . i) NaBH_4 , EtOH, 0°C to RT, 98% over 3 steps. j) I_2 , PPh_3 , imid, RT. k) PPh_3 , MeCN, reflux, 78% over 2 steps.

The newly formed alkene was then efficiently transformed to the primary alcohol **79** in excellent yield. Conversion of alcohol to phosphonium salt **80** via the alkyl iodide proceeded smoothly and afforded the C25-C30 fragment as the Wittig reagent.

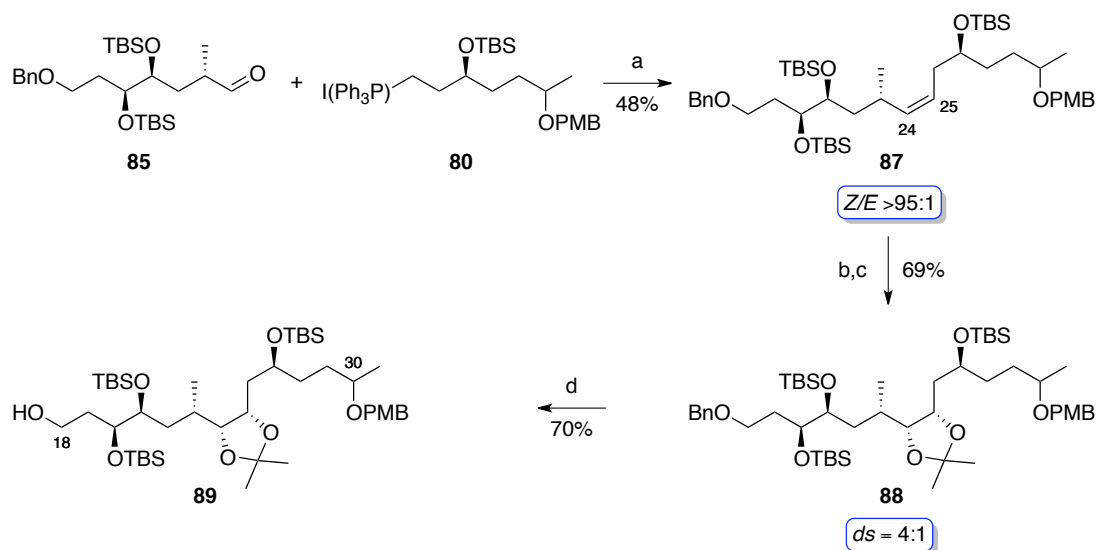
The route to the second Wittig coupling partner **85** is shown in Scheme 3.13.2. Diastereoselective allylation of the Oppolzer's chiral sultam,⁹⁰ followed by the reductive cleavage of the chiral auxiliary with lithium pyrrolidinoborohydride and formation of the primary TBS ether afforded **82** in 74% overall yield. Conversion of the latter to the aldehyde using Hon's ozonolysis conditions,⁹¹ succeeded by condensation with the potassium salt of **86** under Julia-Kocienski conditions,⁷¹ furnished alkene **83** with excellent control over the geometry of double bond (*E/Z* >95:5).

Scheme 3.13.2: Synthesis of Aldehyde **85**

Reaction conditions: a) Allyl bromide, LiHMDS, THF/HMPA, $-78\text{ }^{\circ}\text{C}$. b) LiPyrBH₃, THF, $0\text{ }^{\circ}\text{C}$. c) TBSCl, imid, DMAP, DMF/THF, RT, 74% over 3 steps. d) O₃, DCM, $-78\text{ }^{\circ}\text{C}$, then Et₃N. e) BnO(CH₂)₃SO₂PT (**86**), KHMDS, THF, $-78\text{ }^{\circ}\text{C}$, *E/Z* >95:5, 55% over 2 steps. f) AD-mix- α , ^tBuOH/H₂O, *ds* = 4:1, $0\text{ }^{\circ}\text{C}$. g) TBSOTf, 2,6-lutidine, DCM, $-78\text{ }^{\circ}\text{C}$ to RT, 69% over 2 steps. h) NH₄F, MeOH, $60\text{ }^{\circ}\text{C}$. i) DMP, 79% over 2 steps.

Stereoselective installation of the diol at C20 and C21 was achieved using Sharpless asymmetric dihydroxylation (*ds* = 4:1),⁶⁵ in which the major isomer was isolated and protected as *tris*-TBS ether **84** in 69% yield. Chemoselective deprotection of the primary TBS ether **85** using NH₄F and oxidation using Dess-Martin periodinane⁶⁷ furnished the aldehyde **85** in 79% overall yield (2 steps).

With two coupling partners in hand, the Wittig olefination was carried out to give (*Z*)-alkene **87** as the major product (*Z/E* >95:5) in moderate yield (Scheme 3.13.3). Asymmetric dihydroxylation⁶⁵ of the latter afforded two separable diastereomeric diols with rather low selectivity (*ds* = 4:1). Subsequent acetonide formation and chemoselective hydrogenolysis of the primary benzyl ether using Raney nickel W-4 furnished the C18-C30 fragment **89** of AM3.

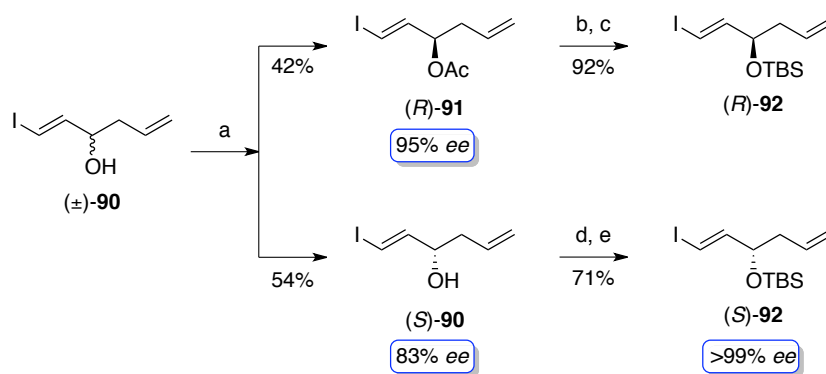
Scheme 3.13.3: Completion of the C18-C30 fragment 89

Reaction conditions: a) KHMDS, toluene, $-78\text{ }^{\circ}\text{C}$, $Z/E > 95:5$, 48%. b) AD-mix- β , $t\text{BuOH}/\text{H}_2\text{O}$, $0\text{ }^{\circ}\text{C}$, $ds = 4:1$, 78%. c) 2,2-DMP, *cat.* CSA, 89%. d) H_2 , Raney Ni W-4, EtOH, RT, 70%.

Overall, Cossy, Marko and co-workers developed a convergent route to the C18-C30 polyol block of amphidinol 3 in 15 longest linear steps with 7.6% overall yield. The highlights of the synthesis include diastereoselective alkylation of the chiral sultam, two Sharpless asymmetric dihydroxylations and allyltitanation as key steps for installation of six stereogenic centres.

3.14 Oishi's and Murata's Synthesis of the C1-C14 Fragment of Amphidinol 3 and its Structural Revision

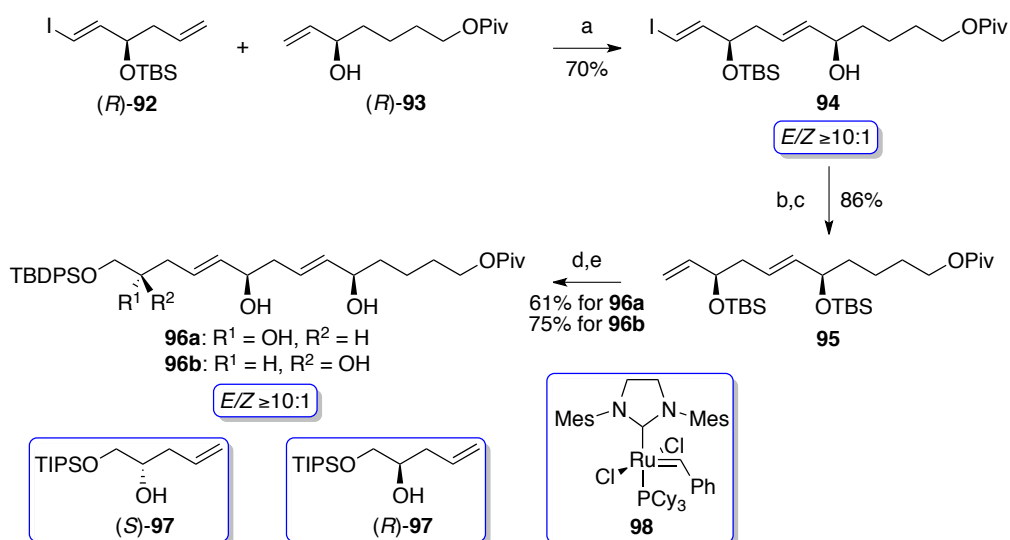
In 2008, Oishi, Murata and co-workers published a combinatorial synthesis of the 1,5-polyol system of amphidinol 3 and its diastereoisomers,⁹² which indicated that in the initial structural elucidation of amphidinol 3 the absolute configuration of the C2 stereocentre was misassigned.^{26a} The synthesis of the polyol segments was designed in such a way that either diastereomer, epimeric at the C2 and C6 positions, could be prepared.

Scheme 3.14.1: Preparation of (*R*)- and (*S*)-92

Reaction conditions: a) Lipase AK, vinyl acetate, 40 °C, 10 h, 95% *ee*, 42% for (*R*)-91, 83% *ee*, 54% for (*S*)-90. b) K₂CO₃, MeOH, 0 °C. c) TBSCl, imid, DMF, 0 °C to RT, 92% over 2 steps. d) Lipase AK, vinyl acetate, 40 °C, >99% *ee*, 86%. e) TBSCl, imid, DMF, 0 °C to RT, 83%.

The racemic alcohol (±)-90 was submitted to the lipase AK catalytic kinetic resolution (Scheme 3.14.1).⁹³ This permitted preparation of the enantioenriched acetate (*R*)-91 in 42% yield, which after protecting group interconversion gave silyl ether (*R*)-92. While the enantiopurity of (*S*)-90 was not satisfactory, it was improved to >99% *ee* by retreatment with lipase AK. Subsequent protection of the latter as a TBS ether afforded (*S*)-92 in good yield.

The polyol segment 96 was elaborated using a cross-metathesis⁸⁴ approach (Scheme 3.14.2). Treatment of (*R*)-92 and (*R*)-93 with catalytic Grubbs 2nd generation carbene 98 afforded coupling product 94 in 70% yield and high selectivity (*E/Z* ≥ 10:1). Palladium catalysed reductive removal of the iodide,⁹⁴ cross metathesis⁸⁴ with (*S*)-97 or (*R*)-97 and consecutive protecting group removal with HF·Py gave diastereoisomers (2*S*,6*R*,10*R*)-96a and (2*R*,6*R*,10*R*)-96b. The preparation of two other diastereomers, (2*S*,6*S*,10*R*)-96c and (2*R*,6*S*,10*R*)-96d, was also achieved in a similar manner (not shown).

Scheme 3.14.2: Synthesis of **96a and its C2 Epimer **96b****

Reaction conditions: a) *cat.* **98**, reflux, $E/Z \geq 10:1$, 70%. b) $n\text{Bu}_3\text{SnH}$, $\text{Pd}(\text{PPh}_3)_4$, benzene, 0 °C to RT, 93%. c) TBSOTf, 2,6-lutidine, DCM, 0 °C to RT, 93%. d) *cat.* **98**, **(S)-97** or **(R)-97**, DCM, reflux, $E/Z \geq 10:1$. e) $\text{HF} \cdot \text{Py}$, THF, 0 °C to 50 °C, 61% for **96a**, 61% for **96b**.

With the four diastereomeric C1-C14 segments (Figure 3.14.1) available, their NMR data was compared to that of the natural amphidinol 3. It was found that the ^1H spectra as well as coupling patterns were indistinguishable, presumably due to remote (1,5-) stereogenic centres.⁹⁵ While alterations in ^{13}C shifts were minute, the deviations at C4 of the 2,6-*syn* isomers (**96b** and **96c**) were lower than those of the 2,6-*anti* isomers (**96a** and **96d**).

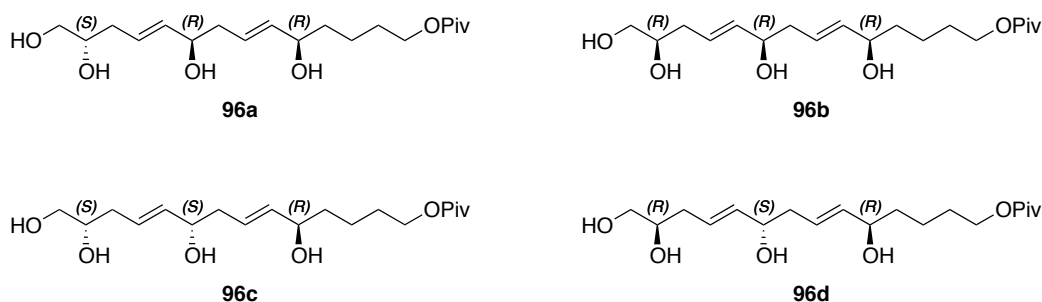
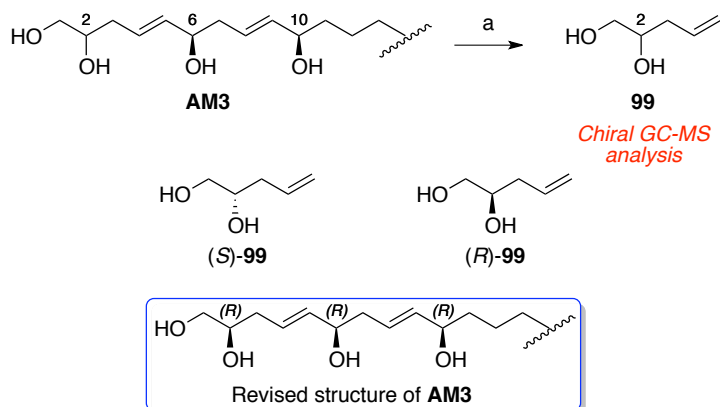


Figure 3.14.1: Structures of the Diastereoisomeric 1,5-Polyols

Based on the fact that absolute configurations at C6 and C10 in the natural product were unambiguously assigned using the modified Mosher's method,²⁸ while that on C2 was deduced by chemical degradation and chiral HPLC analysis, the stereochemistry at C2 became disputable.

In order to solve the problem the authors applied a single-step degradation procedure to amphidinol 3 involving cross-metathesis with ethylene gas (Scheme 3.15.3). With these conditions in hand the degradation product **99** was obtained and analysed by GC-MS using a similar approach to that used in the structural elucidation of maitotoxin.⁹⁶ Based on comparison of the retention times of the authentic samples, the absolute configuration at C2 in the amphidinol 3 was reassigned to be (*R*).

Scheme 3.14.3: Structural Revision of Amphidinol 3

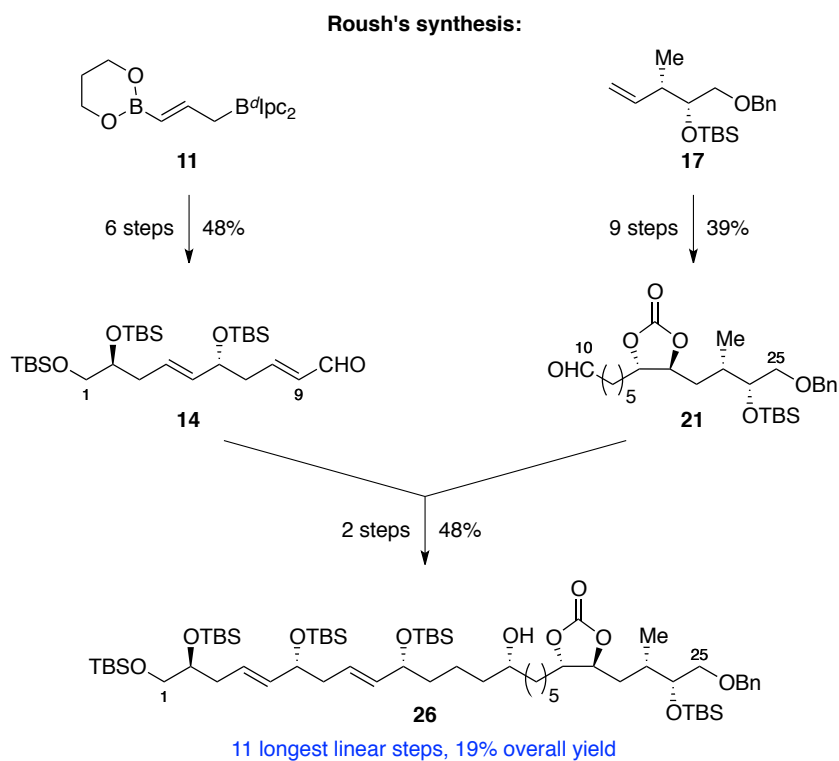
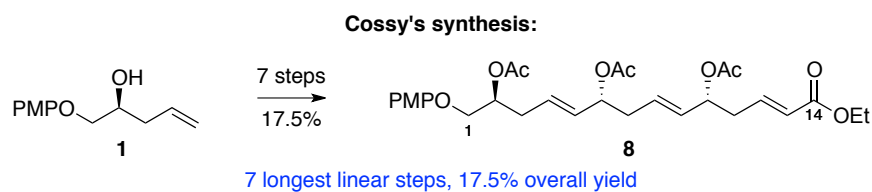


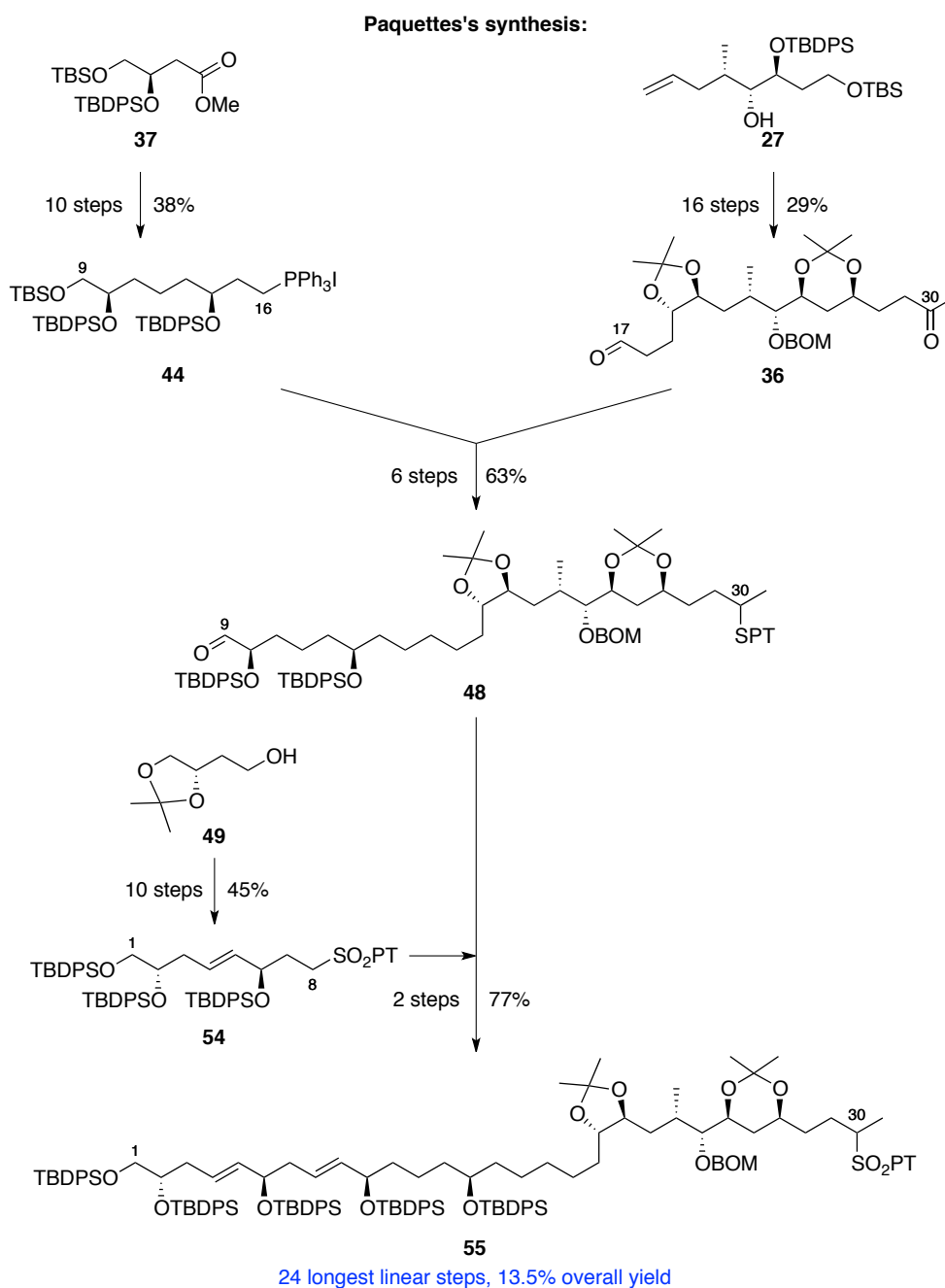
Reaction conditions: a) *cat.* **99**, ethylene, DCM/MeOH (1:1), RT.

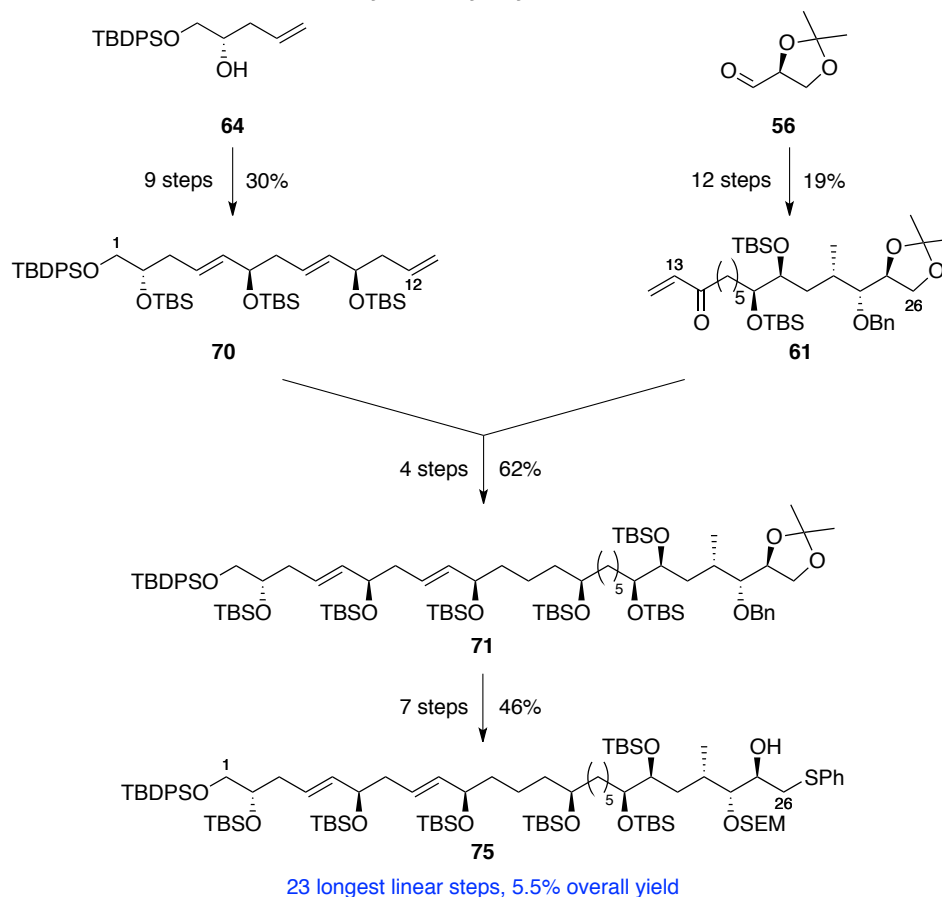
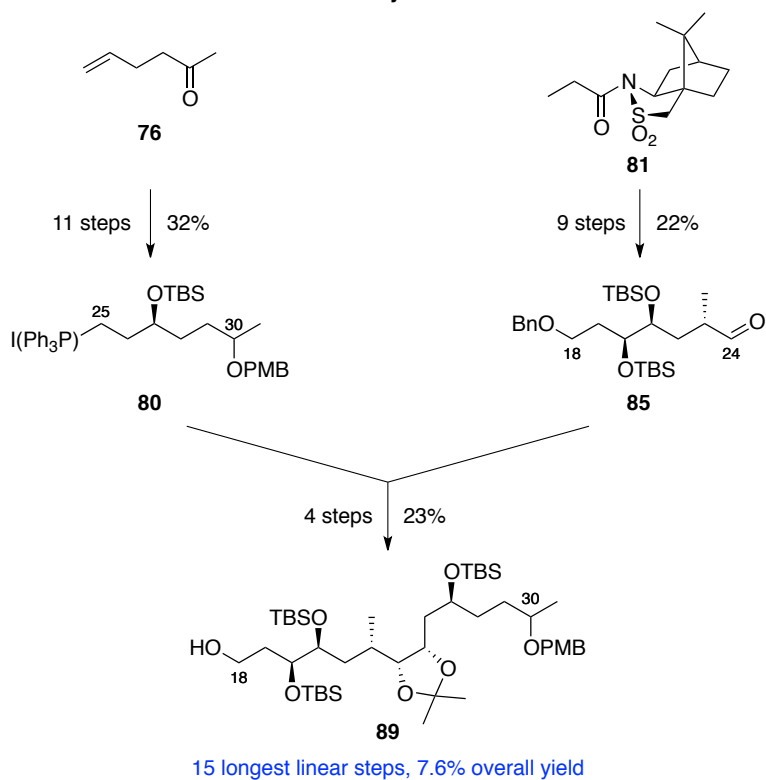
Although the reason of the original misassignment remains unclear, the authors assume that the minute sample size and its contamination with other degradation products led to the erroneous interpretation of the HPLC data.

3.15 Polyol Syntheses Overview

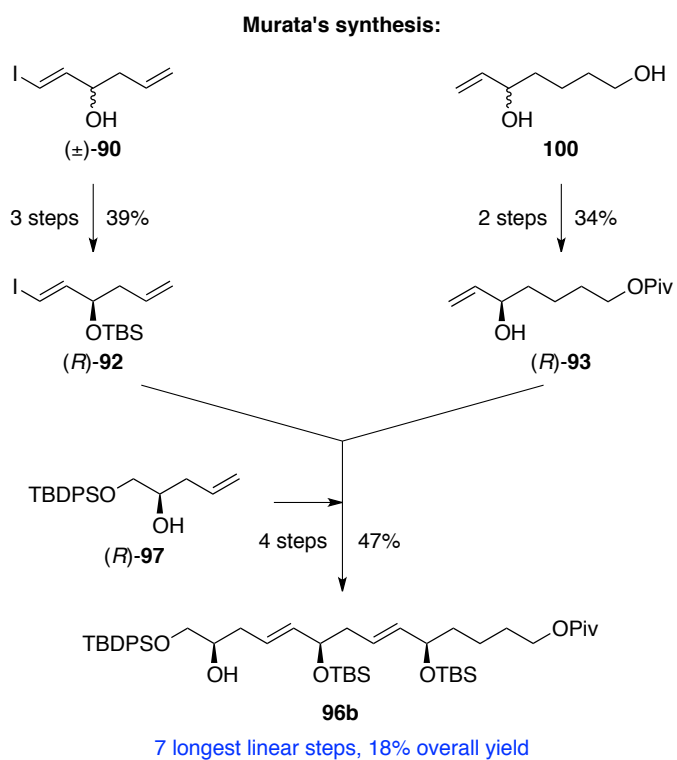
Scheme 3.15.1: Overview of Amphidinol 3 Polyol Fragment Syntheses



Scheme 3.15.2: Overview of Amphidinol 3 Polyol Fragment Syntheses (Cont.)

Scheme 3.15.3: Overview of Amphidinol 3 Polyol Fragment Syntheses (Cont.)**Rychnovsky's synthesis:****Marko's synthesis:**

Scheme 3.15.4: *Overview of Amphidinol 3 Polyol Fragment Syntheses (Cont.)*



3.16 References

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Chapter 4

Synthesis of the Polyol Fragment of Amphidinol 3

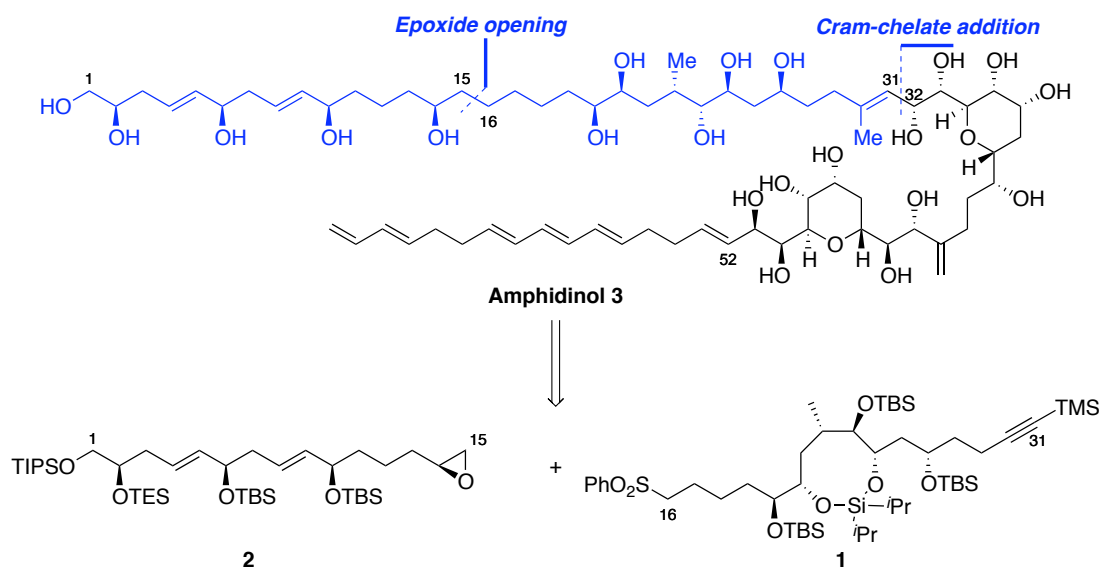
4.1 Introduction

In the course of our studies towards the synthesis of the polyol fragment of amphidinol 3, two approaches were investigated. Both strategies retain the same main disconnections but they differ in the synthetic elaboration of the structural units. The second entry into the polyol overcame the reproducibility issues encountered *en route* and successfully delivered the advanced C1-C31 fragment of amphidinol 3.

4.2 Retrosynthetic Analysis of the Polyol Fragment of Amphidinol 3

The retrosynthetic analysis of the polyol segment of amphidinol 3 is presented in Scheme 4.2.1. We envisaged a highly convergent route to the C1-C31 unit able to deliver a substantial amount of material for the future studies directed towards the union with the C32-C52 fragment and elaboration of the natural product.

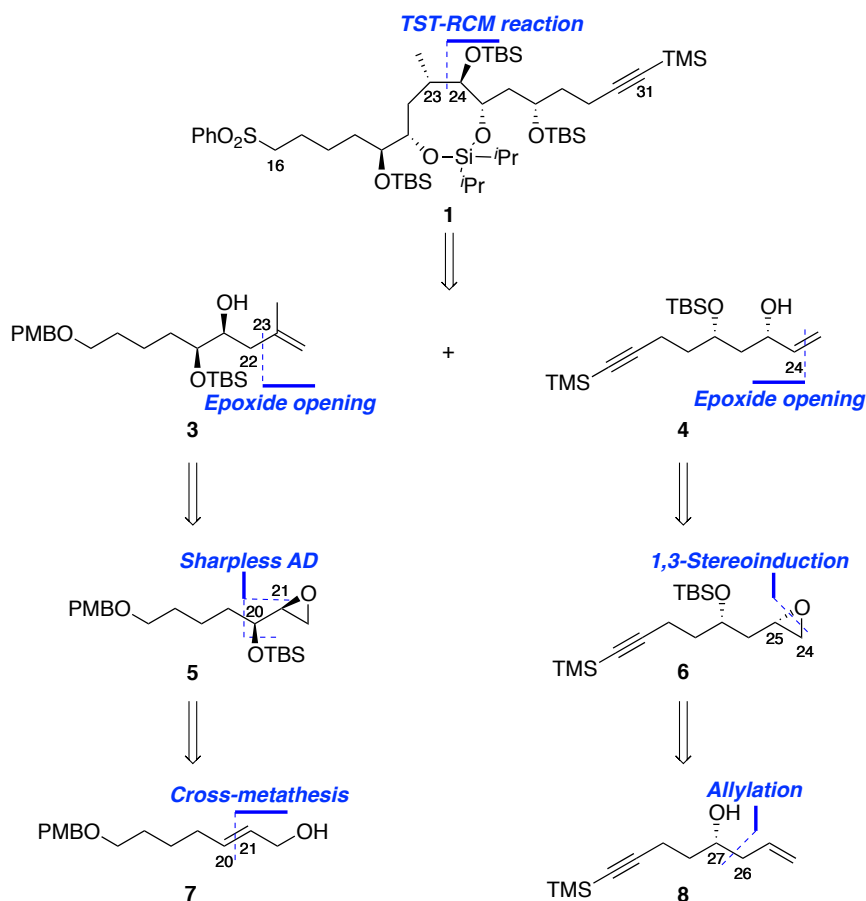
Scheme 4.2.1: Retrosynthetic Analysis of the C1-C31 Fragment of AM3



The strategic disconnection *via* chelate controlled addition at the C31-C32 bond would lead to the C1-C31 fragment and separate it from the *bis*-THP segment. Dissection at the C15-C16 afforded two fragments **1** and **2** for which we planned to use lithiated sulfone addition to an epoxide. The latter strategy has been extensively utilised in the synthesis of the complex natural products and is regarded as a halide-free method of epoxide opening.¹

For the preparation of the cyclic silaketal **1** we envisaged a pivotal disconnection at the C23-C24, which could be constructed using the temporary silicon-tethered ring-closing metathesis (TST-RCM)/hydroboration methodology developed by Alen Cusak in the course of his doctoral studies in the Evans group (Scheme 4.2.2).² The latter dissection would unravel C1-C15 and C16-C31 fragments of similar complexity, each of which contains two stereogenic centres.

Scheme 4.2.2: Retrosynthetic Analysis of Fragment 1

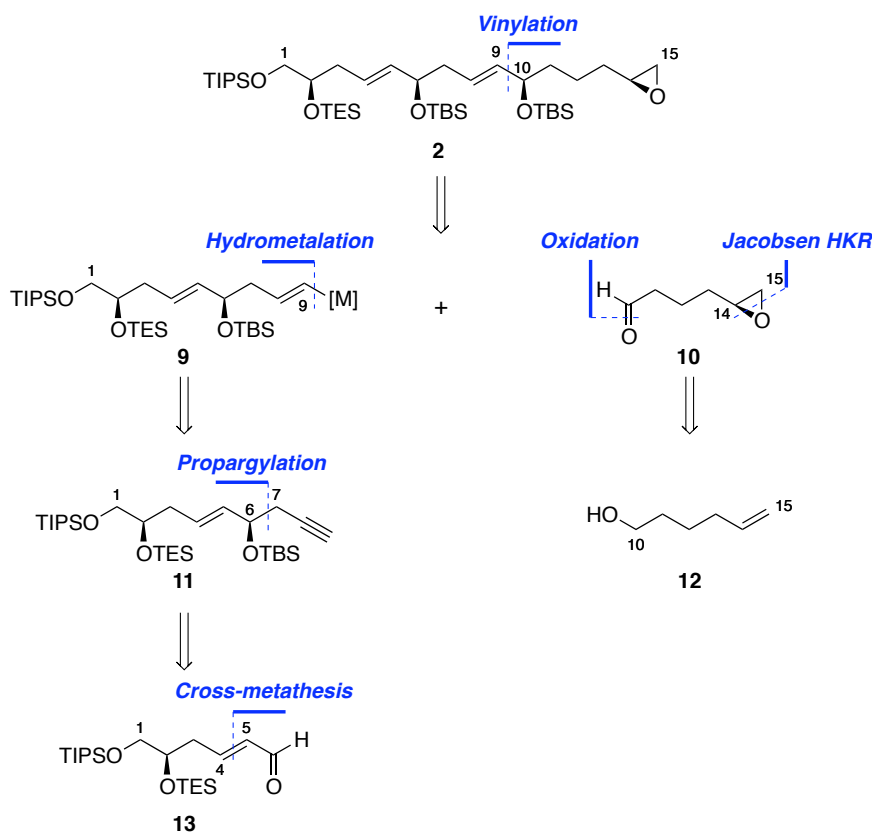


The formation of the homoallylic alcohol **3** could be achieved using alkenyl Grignard addition to epoxide **5**. The incorporation of C20-C21 stereocentres would be effected by Sharpless asymmetric dihydroxylation of the known alkene **7**, which could be accessed *via* cross-metathesis reaction.

In a forward manner, **4** was expected to be available through the epoxide opening of **6** with a sulfonium ylide. The introduction of the C24-C25 epoxide **6** in conjunction with the C25 stereocentre would rely on a substrate controlled 1,3-stereoiduction, while the enantioenriched alcohol **8** could be secured through the asymmetric allylation.

As outlined in Scheme 4.2.3 the major disconnection at C9-C10 could be accessed *via* the stereoselective addition of the vinyl organometallic **9** to the epoxy aldehyde **10**.

Scheme 4.2.3: Retrosynthetic Analysis of Fragment 2

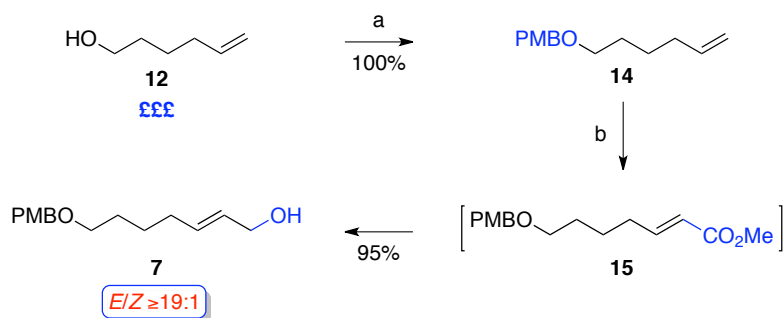


The formation of alkyne **11** was envisaged through the implementation of the challenging asymmetric propargylation of the α,β -unsaturated aldehyde **13**, which in turn could be assembled using a cross-metathesis reaction. The synthesis of fragment **10** would rely on an epoxidation/kinetic resolution and oxidation sequence from alcohol **12**.

4.3 Synthesis of Fragment 3

The construction of the C16-C23 fragment **3** commenced from the commercially available alcohol **12** (Scheme 4.3.1). Primary PMB ether **14**³ formation under basic conditions was followed by cross-metathesis⁴ with excess methyl acrylate, mediated by Hoveyda-Grubbs 2nd generation catalyst,⁵ to give the α,β -unsaturated ester intermediate **15**. The successive *in situ* 1,2-selective reduction using DIBAL-H at -78 °C afforded the known (*E*)-allylic alcohol **7**⁶ in excellent overall yield (95% over 2 steps).

Scheme 4.3.1: Preparation of the (*E*)-Allylic Alcohol **7**

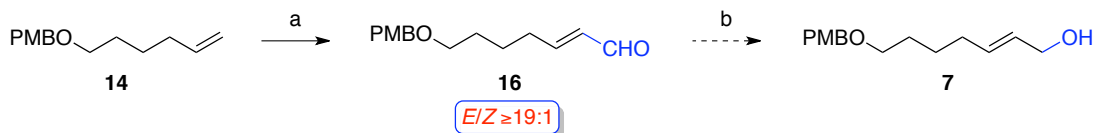


Reaction conditions: a) PMBCl, NaH, DMF, 0 °C to RT, quant.
 b) i. Methyl acrylate, *cat.* HG-II, DCM, 40 °C. ii. DIBAL-H, DCM, -78 °C, 95%, *E/Z* $\geq 19:1$.

It is noteworthy that an alternative route, which featured cross-metathesis⁴ with acrolein and 1,2-Luche reduction⁷ was not viable due to the poor reactivity in

the olefination step, which afforded only 75% conversion after 20 hours with 5 mol% ruthenium carbene loading (Scheme 4.3.2).

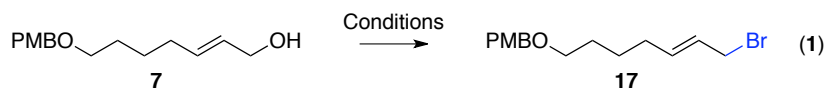
Scheme 4.3.2: *Alternative Approach to 7*



Reaction conditions: a) Acrolein, 5 mol% HG-II, DCM, 40 °C, 20 h, 75% conv., $E/Z \geq 19:1$. b) NaBH_4 , CeCl_3 , MeOH.

The conversion of alcohol **7** to the allylic bromide **17** also proved challenging and required some optimisation (eq. 1, Table 4.3.1). When Appel conditions were applied to alcohol **7** the reaction resulted in an incomplete conversion and formation of side products (entries 1 and 2). Attempts to exploit a one-pot mesylation/Finkelstein substitution sequence⁸ resulted an incomplete conversion in the first step and long reaction times even using a large excess of reagents (entry 3).

Table 4.3.1: *Optimisation of the Allylic Bromide 17 Formation (eq. 1)*



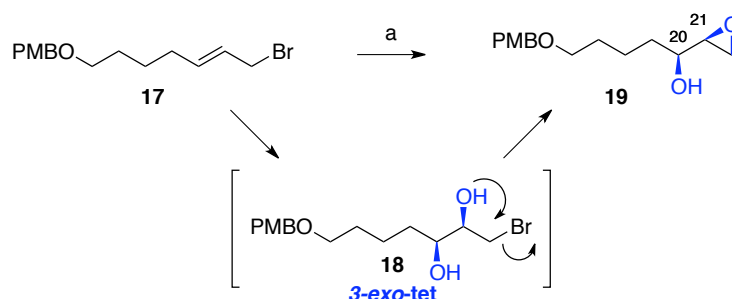
Entry	Conditions	Yield (%) ^a	Notes ^b
1	NBS, PPh_3 , $-20\text{ }^\circ\text{C}$ or $0\text{ }^\circ\text{C}$	48	Incomplete conversion, side products
2	CBr_4 , PPh_3 , $0\text{ }^\circ\text{C}$	50	“
3	MsCl , Et_3N , then LiBr	-	“
4	PBr_3 , Py, $0\text{ }^\circ\text{C}$	69	Clean crude NMR, low yield
5	Br_2 , PPh_3 , imid, 2-methyl-2-butene, $0\text{ }^\circ\text{C}$	quant.	Reverse addition

^aIsolated yield. ^bConversion determined by 500 MHz ^1H NMR analysis of crude reaction mixtures.

Interestingly, halogenation using phosphorus(III) bromide in DCM resulted in full and clean conversion of the alcohol to the desired **17**, but in modest yield (entry 4). Gratifyingly, quantitative formation to the allylic bromide was achieved using a mixture of PPh₃/imid/Br₂ with the reverse addition of the alcohol to a mixture of the preformed phosphonium salt (entry 5).

With the desired bromide in hand, we turned our attention to the installation of the crucial 1,2-*syn* diol moiety at C20-C21. Asymmetric *syn*-dihydroxylation of the allylic bromide **17** using AD-mix- α , following the Sharpless protocol,⁹ afforded the required **19** in 85% yield (Table 4.3.2, entry 1). The transformation proceeds *via* formation of the halohydrin intermediate **18**, which undergoes the *intramolecular* 3-*exo*-tet cyclisation under the basic reaction conditions to result the α -hydroxy epoxide **19**.

Table 4.3.2: Optimisation of the α -Hydroxy Epoxide **19** Formation



Reaction conditions: a) AD-mix- α , ^tBuOH/H₂O (1:1), 0 °C.

Entry ^a	Scale	19/18 ^b	Time, h	Yield (%) ^c
1	0.063 g	1:0	39	85
2	1.25 g	1:2	2	-
3	“	1:1	6	-
4	“	1.6:1	39	47
5^d	“	1:0	21	75

^aAll reactions were carried out using 0.5 mol% of AD-mix- α . ^bRatios of products was determined by 500 MHz ¹H NMR analysis of crude reaction mixtures. ^cIsolated yield. ^dUpon completion of dihydroxylation reaction was quenched with aq. K₂CO₃ and stirred for 8 h.

Unfortunately, the elaboration of this transformation on a larger scale resulted in an inseparable mixture of the desired product **19** and intermediate **18** (entry 2). Based on the observation that longer reaction times produce higher ratios of epoxide (entries 2-4), we in principle could achieve the full conversion of **18** by increasing the transformation time. However, we pursued a different approach. Thus, upon full conversion of **17**, the reaction was quenched with an aqueous solution of K_2CO_3 . This led to smooth cyclisation of the intermediate **18** to epoxide **19** in good overall yield (entry 5). It is notable that no undesired Payne rearrangement product was observed *en route* to **19**.

The stereochemical course of the process was rationalised by assuming that the chiral osmium electrophile was approaching from the bottom face of **17** as suggested by the Sharpless mnemonic (Figure 4.3.1).⁹

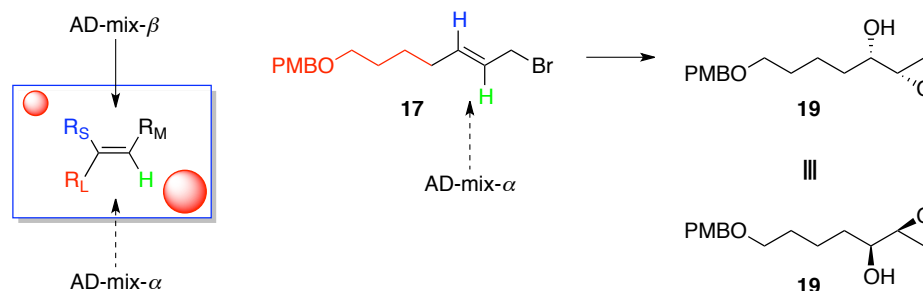
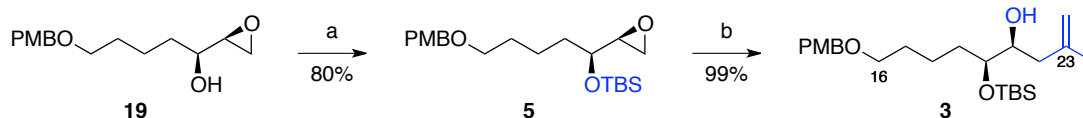


Figure 4.3.1: Sharpless AD Mnemonic Application to Olefin **17**

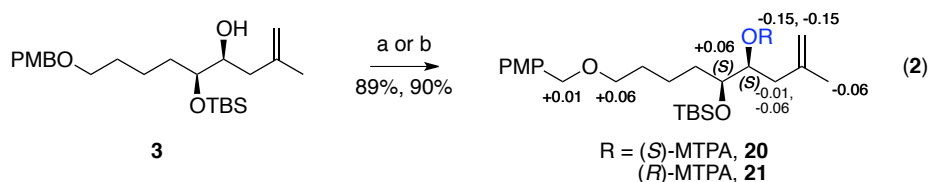
The successive installation of the secondary TBS ether was achieved using TBSCl and imidazole mixture in DMF (80% yield) (Scheme 4.3.3). In contrast, silylation using TBSOTf/2,6-lutidine afforded considerably lower yield (16%) due to the instability of the epoxide moiety under the reaction conditions, even at cryogenic temperatures ($-78\text{ }^{\circ}\text{C}$). Finally, regioselective epoxide opening using isopropenylmagnesium cuprate afforded the C16-C23 fragment of AM3 in quantitative yield.

Scheme 4.3.3: Completion of Fragment 3

Reaction conditions: a) TBSCl, imid, DMF, 0 °C to RT, 80%. b) Isopropenylmagnesium bromide, *cat.* Li₂[CuCl₄], Et₂O, -78 °C to RT, 99%.

4.4 Stereochemistry Proof of Fragment 3

The modified Mosher ester method¹⁰ was used to determine the absolute stereochemistry of C20 and C21 stereocentres in fragment **3**. Ester derivatives were prepared as shown in eq. 2 and the stereochemistry at C21 was unambiguously established as (*S*). Since Sharpless asymmetric dihydroxylation is stereospecific and advances in the suprafacial fashion, the absolute configuration at C20 was assigned as (*S*). Integration of the residual diastereoisomer peaks in the Mosher esters **20** and **21** suggested that asymmetric dihydroxylation of **17** had proceeded with 92% enantiomeric excess.



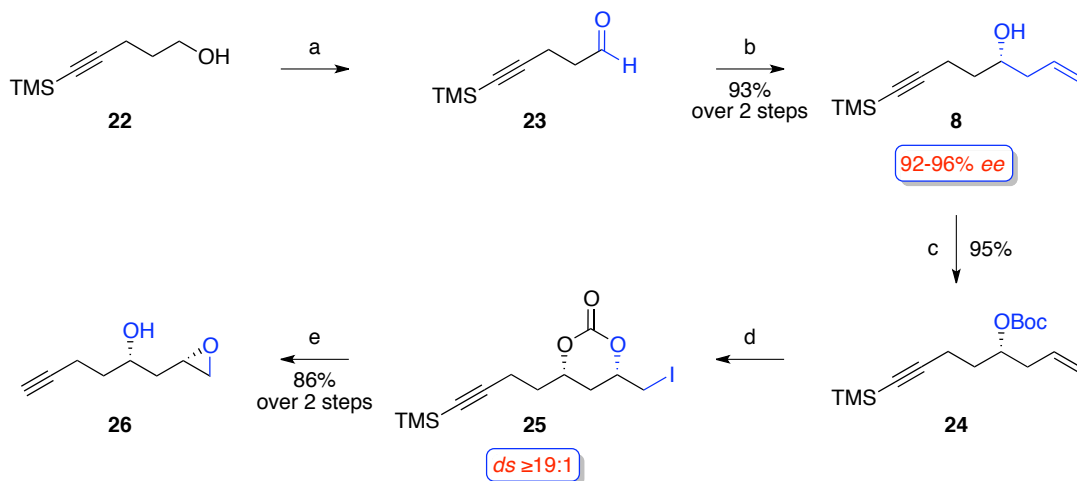
Reaction conditions: a) (*R*)-MTPA-Cl, *cat.* DMAP, Py, DCM, RT, 89%.
b) (*S*)-MTPA-Cl, *cat.* DMAP, Py, DCM, RT, 90%.

4.5 Synthesis of Fragment 4

The synthesis of the C24-C31 fragment **4** began with Swern oxidation¹¹ of the commercially available alcohol **22** (Scheme 4.5.1). By taking advantage of the asymmetric allylation protocol developed by Maruoka *et al.*,¹² the aldehyde **23**¹³ was converted to the homoallylic alcohol **8** using the catalytic chiral *bis*-titanium(IV)

oxide (*R,R*)-**27** and allyltributylstannane with excellent enantiocontrol (92-96% *ee* by chiral HPLC analysis of the benzoate derivative).

Scheme 4.5.1: *Synthesis of the β -Epoxy Alcohol 26*



Reaction conditions: a) $(\text{COCl})_2$, DMSO, DCM, $-78\text{ }^\circ\text{C}$, then Et_3N , $-78\text{ }^\circ\text{C}$ to RT. b) (*R,R*)-**27**, allyl SnBu_3 , DCM, $0\text{ }^\circ\text{C}$, 93% over 2 steps, 92-96% *ee*. c) LiHMDS, BocON, THF, $0\text{ }^\circ\text{C}$, 95%. d) IBr, PhMe, $-85\text{ }^\circ\text{C}$, $ds \geq 19:1$. e) K_2CO_3 , MeOH, RT, 86% over 2 steps.

As outlined in Figure 4.5.1 the complex **28** formation between **23** and the chiral titanium(IV) Lewis acid **27** hinders the *Si*-face of the aldehyde and effects the addition of the stannane nucleophile from the top face *via* the open transition state.¹²

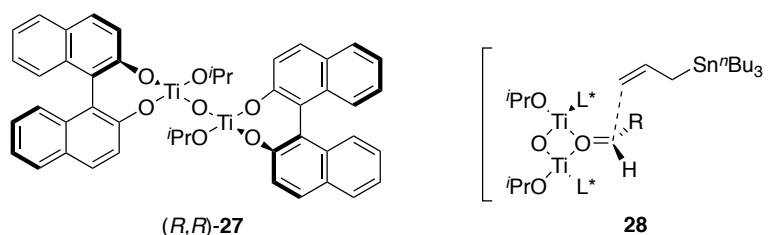


Figure 4.5.1: *Structure of Chiral Bis-Ti(IV) Catalyst and Allylation Transition State*

The formation of the Boc carbonate **24** was then achieved using BocON and LiHMDS as a base in 92% yield. Interestingly, when the protection was carried out using Boc_2O the reaction failed to go to completion and resulted in the recovery of starting material. To effect the strategic substrate controlled 1,3-*syn* stereinduction and install the C25 stereocentre we applied the methodology developed by Barlett¹⁴

and modified by Smith.¹⁵ Towards this end, treatment of **24** with iodine bromide at $-85\text{ }^{\circ}\text{C}$, proceeding through the iodonium intermediate **29**, furnished the unstable cyclic 1,3-*syn*-iodocarbonate **25** with excellent stereocontrol ($ds \geq 19:1$). Subsequent hydrolysis using methanolic K_2CO_3 afforded the β -hydroxy epoxide **26** via a 3-*exo*-tet cyclisation of the intermediate **30** in 86% yield over two steps (Figure 4.5.2). Unfortunately, the basic medium effected the cleavage of the alkyne protective TMS group, which could no be avoided at this stage.

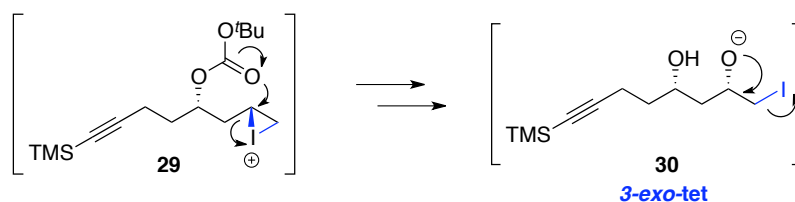
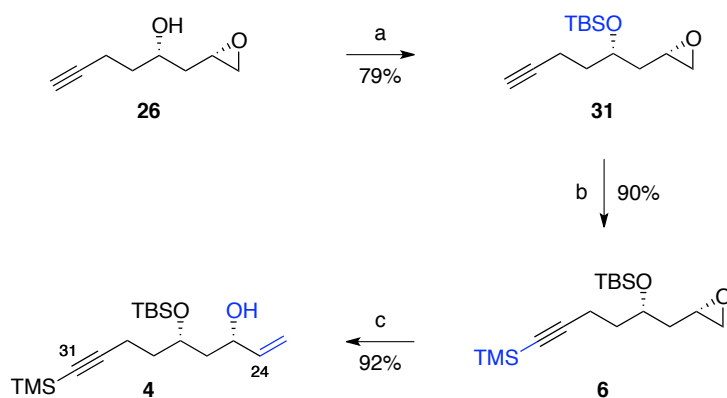


Figure 4.5.2: Iodonium Intermediate **29** and Cyclisation of Iodohydrine **30**

The completion of fragment **4** is presented in Scheme 4.5.2. Protection of the secondary alcohol in **27** as TBS ether and re-introduction of the TMS unit on the alkyne furnished **6** in good overall yield (71% over 2 steps). Addition of the sulfonium ylid, generated *in situ* from Me_3SOTf and $n\text{BuLi}$, to epoxide **6** afforded the allylic alcohol **4**, completing the synthesis of the C24-C31 fragment of amphidinol 3.

Scheme 4.5.2: Completion of Fragment **4**

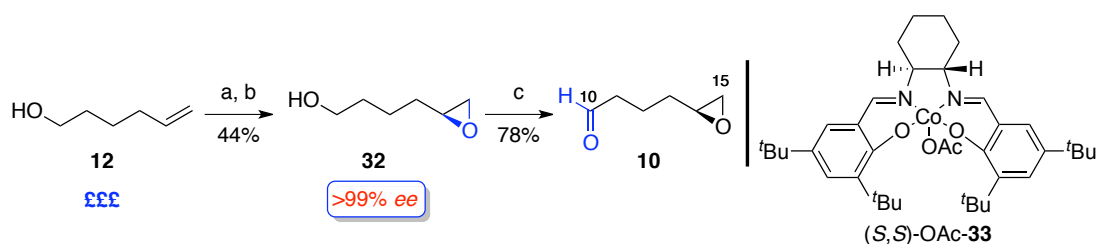


Reaction conditions: a) TBSCl , imid, DMF, $0\text{ }^{\circ}\text{C}$ to RT, 79%.
b) TMSCl , LiHMDS , THF, $0\text{ }^{\circ}\text{C}$, 90%. c) Me_3SOTf , $n\text{BuLi}$, THF, $-10\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$, 92%.

4.6 Synthesis of Fragment 2

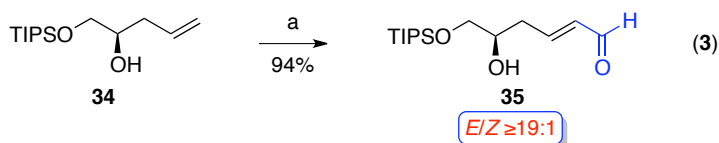
The synthesis of the C1-C15 fragment commenced with the formation of aldehyde **10**, as illustrated in Scheme 4.6.1. Epoxidation of the commercially available alcohol **12** with K_2CO_3 buffered *m*CPBA, followed by Jacobsen's hydrolytic kinetic resolution¹⁶ led to the enantiopure epoxide **32** (enantioselectivity was determined by chiral HPLC analysis of the benzyl ester). The absolute configuration of epoxide **32** was assigned as (*S*) based on the general model of Jacobsen's HKR, implying that (*S,S*)-Co-Salen-OAc catalyst **33** hydrolyses the (*R*) enantiomer of the racemate mixture preferentially. The succeeding oxidation of **32** to the C10-C15 aldehyde **10** was secured under Ley's conditions in 78% yield.

Scheme 4.6.1: Synthesis of Fragment 10



Reaction conditions: a) *m*CPBA, K_2CO_3 , DCM, 0 °C to RT, 76%. b) (*S,S*)-OAc-**33**, H_2O , THF, 0 °C to RT, 58% (based on 50% conv.), >99% *ee*. c) TPAP, NMO, 4 Å MS, DCM, 0 °C, 78%.

The construction of the C1-C9 unit of amphidinol 3 was initiated with the highly selective (*E/Z* ≥ 19:1) cross metathesis⁴ of the known homoallylic alcohol **34**¹⁷ with acrolein mediated by Hoveyda-Grubbs 2nd generation catalyst (eq. 3).⁵



Reaction conditions: a) Acrolein, 1 mol% HG-II, DCM, 40 °C, 94%, *E/Z* ≥ 19:1.

The protection of the hydroxyenal system in **35** was then investigated (eq. 4, Table 4.6.1). Based on the overall protecting group strategy, we envisaged masking the majority of the secondary alcohols in the molecule as TBS ethers. Unfortunately, all efforts to install the latter functionality in **35** with high yield failed. We screened a range of the silyl electrophile sources and bases, but in all instances the incomplete conversion was observed in conjunction with the inseparable by-products (entries 1-6). Careful analysis of the reaction mixtures suggested that the main side product of the TBS protection was the persilylated enol ether **37**. Furthermore, the reduced yield of **36** was attributed to the Mukaiyama aldol reaction, which could in principle take part between **37** and the starting material **35** or enal **36**.

Table 4.6.1: *Optimisation of the Hydroxyenal **35** Silylation (eq. 4)*

TIPSO-CH2-CH(OH)-CH=CH-CHO (35) $\xrightarrow{\text{Conditions}}$ TIPSO-CH2-CH(OR)-CH=CH-CHO (36/13) + TIPSO-CH2-CH(OR)-CH=CH-CH(OR) (37/38)

R = TBS **36**
 R = TES **13**

(4)

Entry	Conditions	Yield (%), (conv., %) ^{a,b}	Notes ^b
1	TBSOTf, Et ₃ N, DCM, -78 °C	75(88)	Trace of 37
2	TBSOTf, 2,6-lutidine, DCM, -78 °C	-(79)	<2% of 37
3	TBSOTf, pyridine, DCM, -78 °C	-(85)	36/37 – 10:1
4	TBSCl, imid, DMF, 0 °C	decomp.	-
5	TBSCl, DIPEA, DMF, 0 °C	“	-
6	TBSCl, DMAP, DCM, 0 °C	“	-
7	TESOTf, Et₃N, DCM, -78 °C	99	13/41 – 1:0

^aIsolated yield. ^bConversion and products ratio determined by 500 MHz ¹H NMR analysis of crude reaction mixtures.

The observed experimental data suggested that the main reason of the low efficiency of TBS protection was the limited steric accessibility of alcohol vs. enol functionality (Figure 4.6.1). The issue was successfully circumvented by using less

sterically demanding TESOTf, which delivered **13** in essentially quantitative yield without the concomitant formation of the persilylated product **38** (entry 7). Although, the introduction of the relatively labile secondary TES ether was potentially problematic, we expected that the steric bulk of the neighbouring TIPS moiety could account for the greater stability of the latter throughout the synthesis.

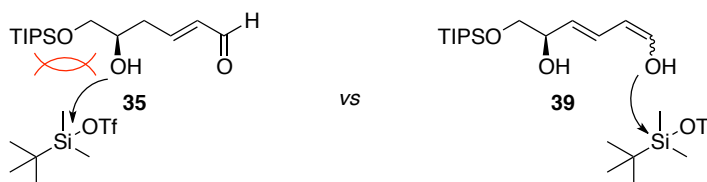


Figure 4.6.1: *Steric Clash in Hydroxyenal vs Dienenol*

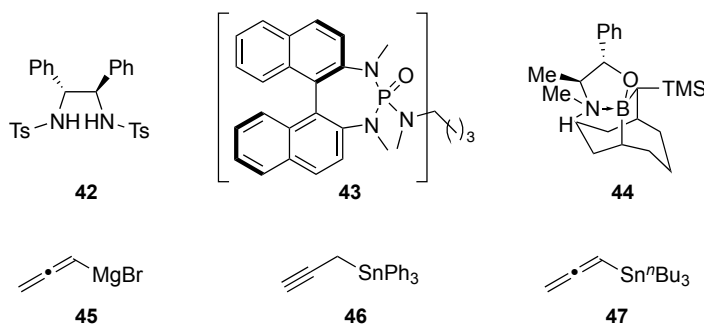
With a reliable route to access the protected enal **13**, we set out to stereoselectively introduce the homopropargyl functionality and complete the C1-C9 fragment of AM3. Much to our surprise, the asymmetric propargylation of the α,β -unsaturated aldehyde **13** proved to be extremely problematic. As outlined in Table 4.5.2, propargylation of **36** under Barbier conditions afforded **40** with nearly 1:1 ratio of diastereoisomers (entry 1). Unfortunately, application of Maruoka's chiral *bis*-Ti(IV) catalyst with allenyl stannane **47**¹⁸ led to complete recovery of the starting material, presumably due to low electrophilicity of the aldehyde, deactivated by conjugation (entry 2). Similarly, a Ti(IV)-based system developed by Yu¹⁹ was unreactive (entry 3). Next, we turned our attention to the base-activated chirally modified Lewis acid, SiCl₄, introduced by Denmark.²⁰ Initial experiments gave us some hope by affording the 23% of the desired propargylation product **40** and the intact starting material (entry 4). However, attempts to improve the reactivity by the increased loading of the phosphoramidate ligand **43** and tin nucleophile **47** were futile (entry 5).

Table 4.6.2: *Optimisation of the Asymmetric Propargylation (eq. 5)*

Entry	Substrate	Conditions	<i>ds</i> ^a	Yield (%) ^b
1	36	Zn, propargyl bromide, THF/aq. NH ₄ Cl	55:45	79 (94 b.r.s.m.)
2	“	Ti(O ^{<i>i</i>} Pr) ₄ , TiCl ₄ , Ag ₂ O, (<i>R</i>)-BINOL, 47	n/r	n/r
3	“	Ti(O ^{<i>i</i>} Pr) ₄ , (<i>R</i>)-BINOL, B(OMe) ₃ , 4Å MS, 47	“	“
4	“	SiCl ₄ , 5 mol% (<i>R</i>)- 43 , 1.1 equiv of 47	n/d	23 (90 b.r.s.m.)
5	“	SiCl ₄ , 10 mol% (<i>R</i>)- 43 , 2 equiv of 47	n/d	30 (87 b.r.s.m.)
6	13	1.2 equiv of 44, 1.2 equiv of 45	>99:1	65
7	13	BBr₃, 1.05 equiv of 42, 1.1 equiv of 46	>99:1	75

^aDiastereomeric ratio determined by chiral HPLC of the benzoate derivative. ^bIsolated yield.

Further examination of the major asymmetric propargylation methodologies revealed that the stereoselective formation of **41** could only be achieved by the application of the stoichiometric chiral boronates, introduced by Corey²¹ and Soderquist²² (entries 6 and 7).

**Figure 4.6.2:** *Structures of Nucleophiles and Chiral Ligands Used for the Asymmetric Propargylation*

Gratifyingly, these reactions furnished **41** with 75% and 65% yield respectively and excellent facial selectivity ($ds \geq 99:1$). Both reactions were assumed to proceed through cyclic boat-type transition states **48** and **49**, which resulted in the *intramolecular* delivery of the allenyl nucleophile from the less sterically congested *Re*-face of the aldehyde and formation of the (*S*)-configured secondary homoallylic alcohol **41** (Figure 4.6.3).

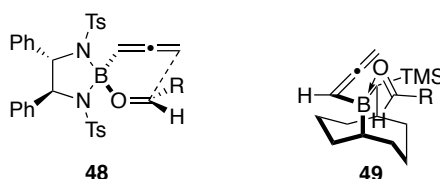
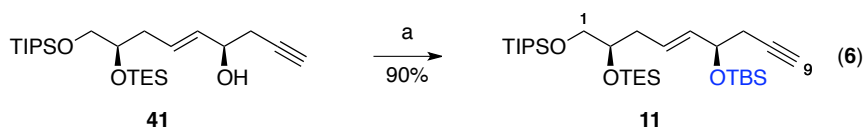


Figure 4.6.3: Transition States for the Propargylation Reaction of **13**

Ultimately, the synthesis of the C1-C9 fragment was completed by the TBS protection of the newly generated secondary alcohol at C6 in excellent yield (eq. 6).

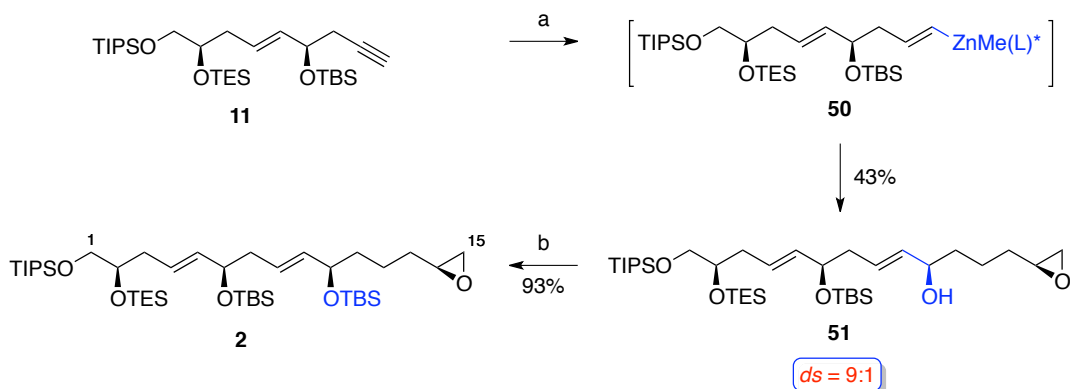


Reaction conditions: a) TBSOTf, Et₃N, DCM, -78 °C, 90%.

With a reliable route to **11** available, we pursued its strategic coupling with the C10-C15 unit **10** and access the C1-C15 segment of amphidinol 3. We planned to achieve this union by performing the asymmetric vinylation using the organozinc chemistry developed by the Wipf and Walsh research groups.²³ Thus, generation of the chiral vinyl zincate **50** was carried out by a chemoselective hydrozirconation of alkyne **11** with Schwartz's reagent, followed by transmetalation with dimethylzinc and addition of the chiral (-)-MIB ligand (Scheme 4.6.2). Treatment of the latter with aldehyde **10** afforded the allylic alcohol **51** in 43% unoptimised yield and with good diastereocontrol ($ds = 9:1$). Finally, TBS protection of the secondary alcohol

51 using TBSOTf and 2,6-lutidine mixture at $-78\text{ }^{\circ}\text{C}$ delivered the C1-C15 fragment **2** in excellent yield.

Scheme 4.6.2: Synthesis of Fragment 2



Reaction conditions: a) i. $\text{Cp}_2\text{Zr(H)Cl}$, DCM, $0\text{ }^{\circ}\text{C}$. ii. Me_2Zn , $(-)\text{-MIB}$, DCM, $-78\text{ }^{\circ}\text{C}$ to RT. iii. **10**, DCM, $-10\text{ }^{\circ}\text{C}$, 43%, $ds = 9:1$. b) TBSOTf, 2,6-lutidine, DCM, $-78\text{ }^{\circ}\text{C}$, 96%.

The stereochemical outcome of the vinylation step could be explained using the Noyori model **52** (Figure 4.6.4).²⁴ Formation of the rigid bicyclic bimetallic transition state *via* coordination of the carbonyl to the more Lewis-acidic Zn atom allowed for the activation of the former towards the vinyl transfer to the *Si*-face of the aldehyde and furnished the allylic alcohol **51** with (*R*)-configuration.

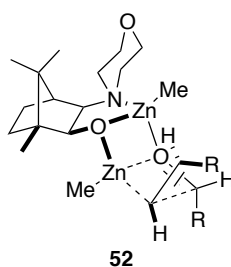


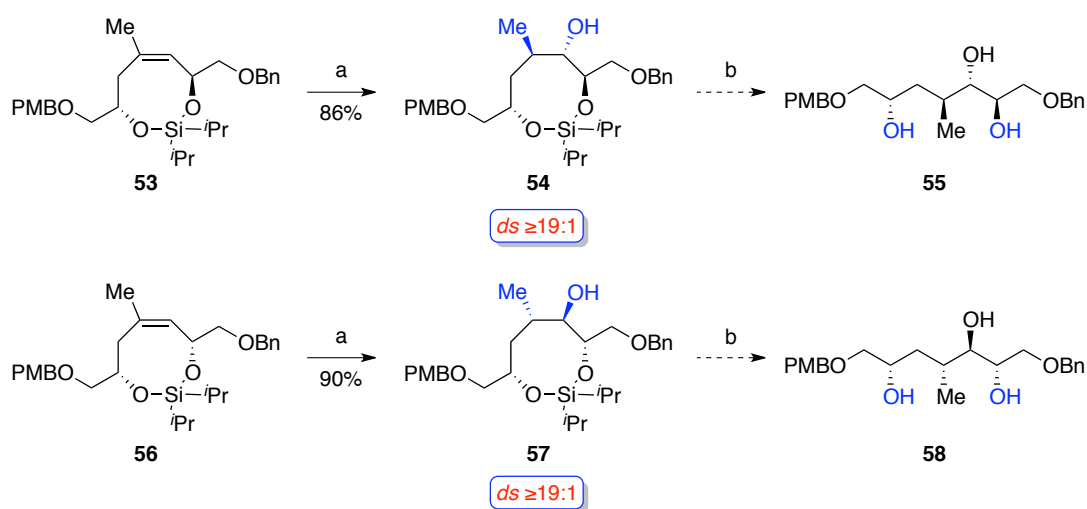
Figure 4.6.4: Noyori's Model for the Vinylation Transition State

4.7 Synthesis of Fragment 1

During the course of doctoral studies in the Evans laboratory, Alen Cusak demonstrated that eight-membered cyclic *syn*- and *anti*-silaketals undergo a highly stereoselective hydroboration reaction to deliver propionate motif containing units

(Scheme 4.7.1).² The facial selectivity of the borane addition was shown to be dictated by the absolute configuration of the allylic ether and proceeded from the less sterically hindered face of the silyl ketal. The stereochemical outcome of the transformation was unambiguously proved by the combination of the modified Mosher esters and X-ray analysis. Furthermore, the fluoride based deprotection of the hydroboration products could unravel diastereomeric propionate units, which are found within the structural frameworks of many biologically important natural products, *e.g.* spirastrellolide A and F methyl esters, fumonisins B1 and baconipyrones C (Figure 4.7.1).²⁵

Scheme 4.7.1: Model Hydroboration of *syn*- and *anti*-Silaketals



Reaction conditions: a) $\text{BH}_3 \cdot \text{DMS}$, THF, RT, then $\text{NaOH}/\text{H}_2\text{O}_2$, 0 ° C to RT, 86% and 90%, $ds \geq 19:1$. b) TBAF, THF.

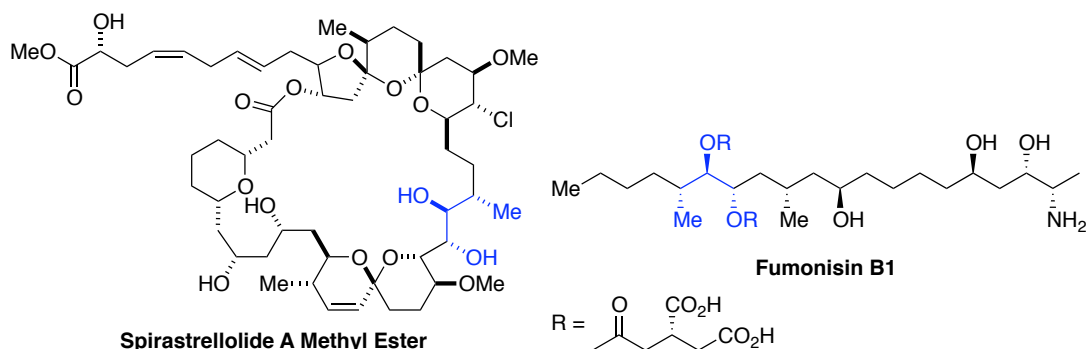
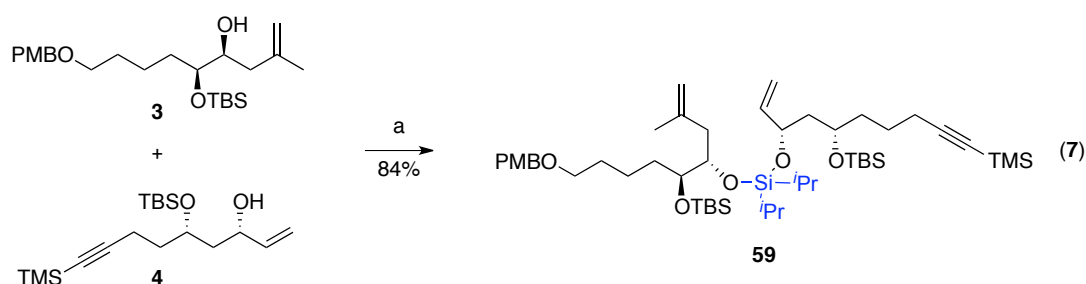


Figure 4.7.1: Natural Products with Polypropionate Units

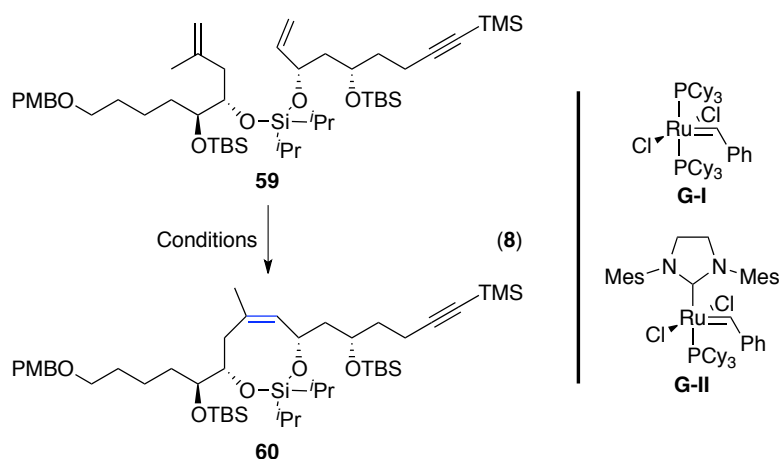
We envisaged that this methodology could provide us with a convenient avenue to access the C16-C31 segment of AM3 with the concomitant installation of the crucial C23-C24 stereocentres. The synthesis of fragment **1** began with the formation of the advanced mixed silaketal **59**, which was achieved in 84% yield from alcohols **3** and **4** with the implementation of $i\text{Pr}_2\text{SiCl}_2$ as a temporary silicon tether (TST) (eq. 7).



Reaction conditions: a) **3**, $i\text{Pr}_2\text{SiCl}_2$, imid, 0 °C to RT, then **4**, imid, DCM, 0 °C to RT.

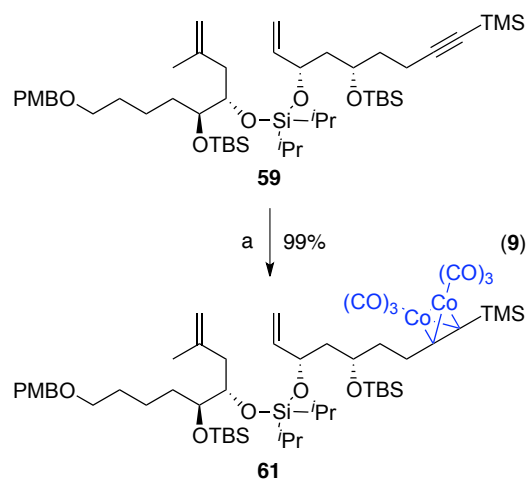
With gram quantities of **59** in hand we moved to the investigation of RCM reaction (eq. 8, Table 4.7.1). Our initial efforts were based on conditions used by Dr. Cusak for synthesis of the cyclic silaketals **53** and **56**. Unfortunately, no conversion to the desired product was observed using Grubbs 2nd generation catalyst with loadings up to 30 mol% (entry 1). The complete substrate recovery was observed when the reaction was run at a higher temperature in benzene (entry 2). Following the report of Grela *et al.* that fluorinated solvents increase the catalyst's turnover in metathesis reactions,²⁶ we switched to perfluorotoluene, but formation of **60** was not observed (entry 3). Finally, application of other ruthenium carbenes proved to be ineffective as well (entries 4 and 5).

Table 4.7.1: *TST-RCM Reaction of 59 (eq. 8)*



Entry	Catalyst	Conditions	Conc. (mM)	Time (h)	Yield (%)
1	30 mol% G-II	40 °C, DCM	9.5	24	-
2	“	80 °C, PhH	“	72	-
3	“	80 °C, C ₆ F ₆ CF ₃	“	48	-
4	30 mol% G-I	40 °C, DCM	“	24	-
5	30 mol% HG-II	“ , “	“	“	-

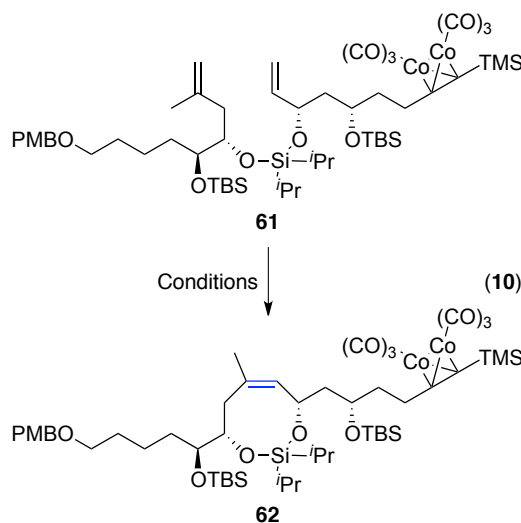
Although it is known that the metathesis reaction is tolerant to the presence of the electron rich triple bond,²⁷ it was likely that in our case the alkyne was inhibiting the catalytic system. According to the literature, a cobalt carbonyl complex could be an effective and easily removable group for the protection of alkynes interfering with metathesis process.²⁸ To test the feasibility of the approach, the alkyne-cobalt complex **61** was formed under standard conditions (eq. 9).



Reaction conditions: a) $\text{Co}_2(\text{CO})_{10}$, DCM, RT, 99%.

Subsequent attempts to optimise TST-RCM reaction on the substrate **61** bearing a masked alkyne are illustrated in Table 4.7.2. Initial investigation of various ruthenium carbene catalysts led to the recovery of the starting material, along with the cobalt complex decomposition to afford alkyne **59** (entries 1-4). Interestingly, while 30 mol% of Grubbs 2nd generation catalyst resulted in no reaction, stoichiometric quantities of the latter resulted in 54% conversion to the desired alkene **62**, along with 11% of dimer and substantial decomposition to **59**. The reactivity was slightly improved at higher temperatures and prolonged reaction times. This led to a better product distribution, but the complete cobalt complex decomposition was detected (entry 6).

Table 4.7.2: *Optimisation of the RCM Reaction of 61 (eq. 10)*



Entry ^a	Catalyst	Conditions	Time (h)	Yield (%) ^{b,c}
1	30 mol% G-I	40 °C, DCM	48	– ^d
2	30 mol% HG-II	–, –	“	– ^d
3	1 eq. HG-II	–, –	24	– ^d
4	30 mol% G-II	–, –	“	– ^d
5	1 eq. G-II	–, –	17	54% conv., 42% of 62 , 11% of dimers, 61/59 -1.6:1
6	30 mol% G-II	100 °C, PhMe	48	Full 61 decomp., 50% conv., 89% of 62 , 11% dimers

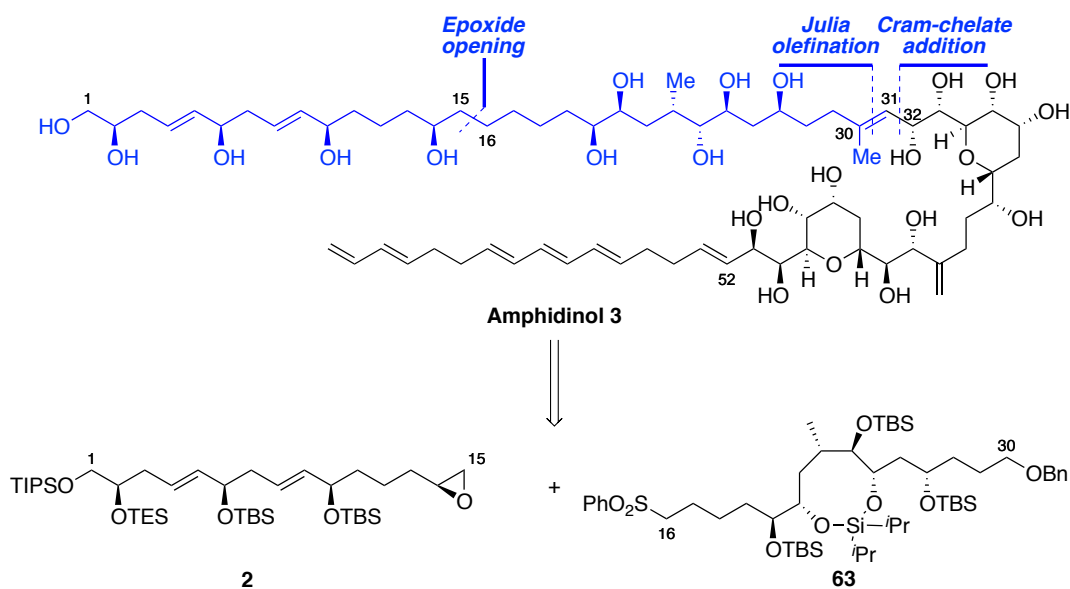
^aAll reactions were carried out at 9.5 mM concentration. ^bIsolated yield. ^cDiastereomeric ratio and conversion determined by 500 MHz ¹H NMR analysis of crude reaction mixtures. ^dRecovered starting material, some complex decomp.

Based on the observed results it was inferred that TST-RCM reaction is viable at elevated temperatures and high Grubbs 2nd generation catalyst loading. However, the cobalt-alkyne complex **61** was not stable at these conditions and was decomposing to the alkyne, which in turn shuts down the catalytic cycle by irreversibly binding to the ruthenium carbene. Therefore, from a strategic standpoint, synthesis of a metathesis precursor without the interfering alkyne moiety could improve the catalyst turnover and provide the desired TST-RCM product.

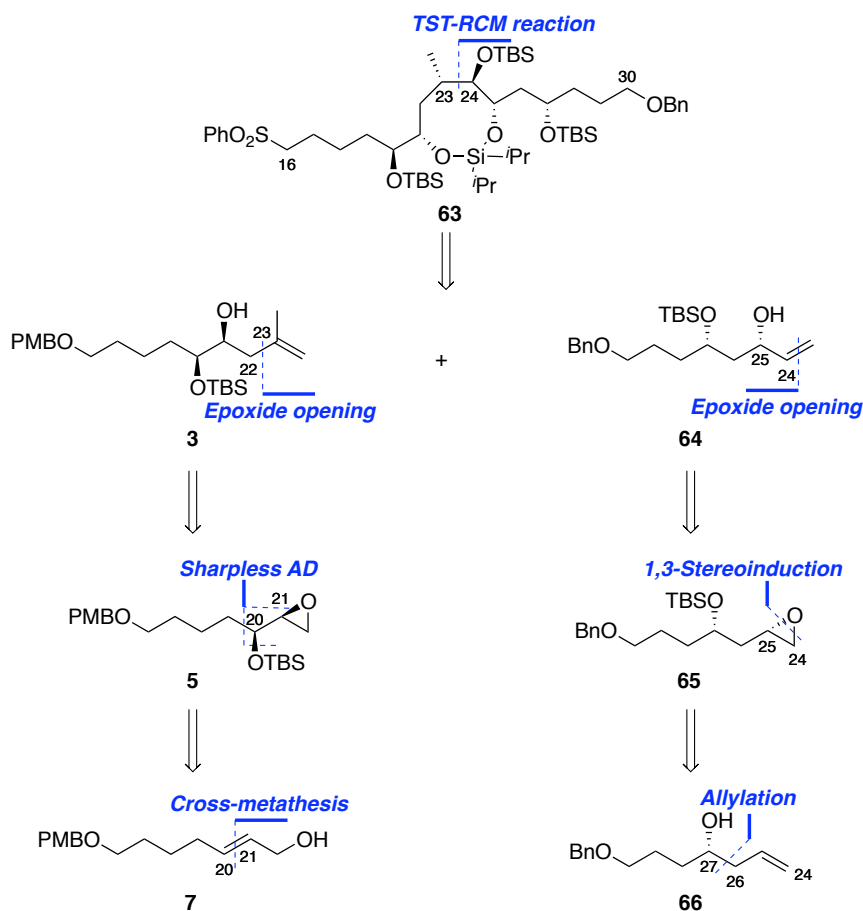
4.8 Revised Approach to the C16-C30 Fragment of Amphidinol 3

Difficulties encountered during the strategic TST-RCM reaction led us to reinvestigation of the strategic plan towards the polyol segment of AM3 (Scheme 4.8.1). We envisaged a new disconnection at C30-C31, which could be obtained *via* Julia-type olefination. This approach would add a high degree of flexibility to the route, since the benzyl ether in fragment **63** could act as both olefination precursor (in the form of sulfone or ketone) or as a masked alkyne, available *via* deprotection, oxidation and Seyferth–Gilbert homologation.²⁹ Thus, leaving the opportunity to exploit a chelation-controlled C31-C32 bond formation.

Scheme 4.8.1: Revised Retrosynthetic Analysis of the C1-C30(31) Fragment of AM3



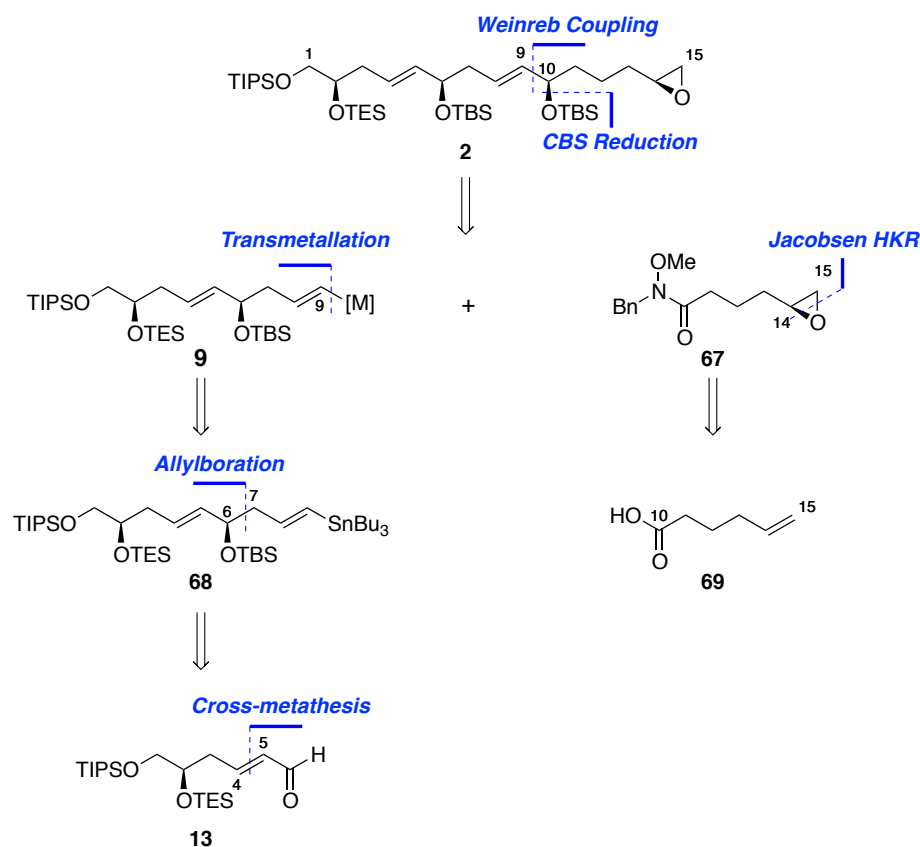
By analogy to the previous analysis, the main disconnection at C15-C16 should provide epoxide **2** and sulfone **63**. The synthetic strategy towards the C16-C30 fragment should not change and in a retrosynthetic manner **63** could be unravelled to alcohols **3** and **64** (Scheme 4.8.2). The latter would come from the sulfonium ylid addition to epoxide **65**. Whereas, IBr mediated 1,3-*syn* stereoinduction and asymmetric allylation would give **65** and **66** respectively.

Scheme 4.8.2: Revised Retrosynthetic Analysis of Fragment 63**4.9 Revised Approach to the C1-C15 Fragment of Amphidinol 3**

Although the developed route to the C1-C15 fragment of amphidinol 3 delivered acceptable quantities of material for epoxide opening studies, we experienced certain difficulties during the scale-up procedure. Mainly, problems arose in the asymmetric propargylation step, which produced inconsistently low yields (30-50%) of **41** due to the deprotection of silyl ethers by the residual HBr (generated during the chiral boronate formation). Additionally, we did not see any means to improve the moderate selectivity of the vinylation step. Therefore, we pursued an alternative and more selective route to this fragment, capable to deliver larger quantities of the material. The revised strategy is depicted in Scheme 4.9.1.

We decided to maintain the high convergence of the route by keeping the pivotal disconnection at the same place. The asymmetric allylboration reaction developed by Roush³⁰ was chosen to substitute for the C6-C7 bond forming propargylation step. In a forward manner, the C10-C15 fragment of AM3 was anticipated to come from the commercially available acid **69**. Subsequently, Weinreb amide coupling should be the ultimate bond forming reaction between the C1-C9 and C10-C16 units. Whereas, CBS reduction was planned to secure the installation of the C10 stereocentre and furnish **2** after TBS protection.

Scheme 4.9.1: Revised Retrosynthetic Analysis of Fragment **2**

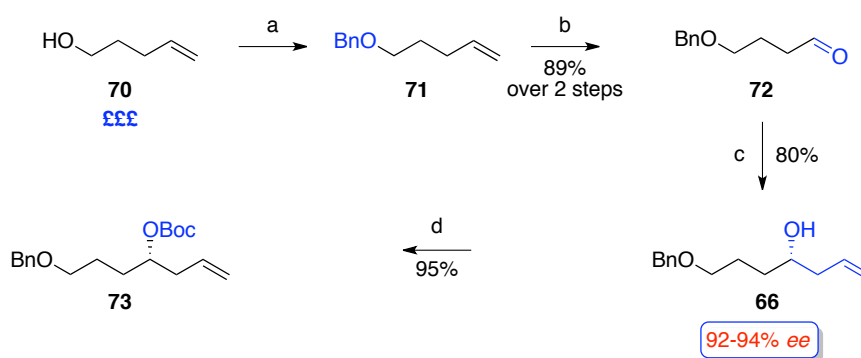


4.10 Revised synthesis of the C24-C30 Fragment of Amphidinol 3

The improved synthesis of the C24-C30 fragment delineated from the commercially available alcohol **70** (Scheme 4.10.1). Protection of the later as a

benzyl ether followed by ozonolysis furnished aldehyde **72** in 89% yield ready for the installation of the first stereocentre. By taking advantage of Maruoka's asymmetric allylation protocol,¹² aldehyde **72** was converted to the known homoallylic alcohol **66**³¹ using catalytic chiral *bis*-titanium(IV) oxide (*R,R*)-**27** and allylSnBu₃ with excellent enantiocontrol (92-94% *ee* by chiral HPLC analysis).

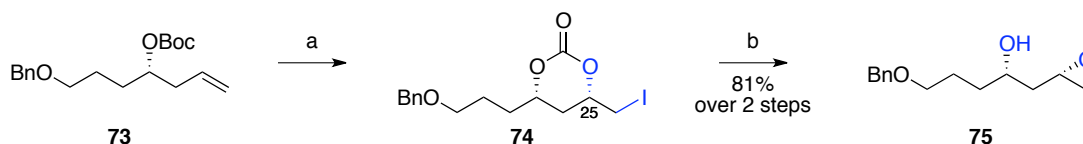
Scheme 4.10.1: Synthesis of the Boc Carbonate **73**



Reaction conditions: a) BnBr, NaH, DMF, 0 °C to RT. b) O₃, DCM, -78 °C, then PPh₃, -78 °C to RT, 89% over 2 steps. c) (*R,R*)-**27**, allylSnBu₃, DCM, 0 °C, 80%, 92-94% *ee*. d) BocON, LiHMDS, THF, 0 °C, 95%.

The formation of the Boc carbonate **73** was then achieved using BocON and LiHMDS as a base in 95% yield. The strategic substrate-directed 1,3-*syn* stereoinduction in carbonate **73** was achieved using IBr at low temperature to furnish **74** and install the C25 stereocentre with good diastereocontrol (*ds* = 15:1) (Scheme 4.10.2). Subsequent hydrolysis of **74** using methanolic K₂CO₃ afforded the β -hydroxy epoxide **75** in 81% yield over two steps.

Scheme 4.10.2: Synthesis of the β -Hydroxy Epoxide **75**

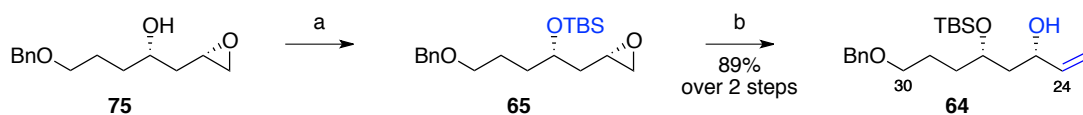


Reaction conditions: a) IBr, PhMe, -85 °C, *ds* = 15:1. b) K₂CO₃, MeOH, RT, 81% over 2 steps.

It is noteworthy that the hydrolysis reaction time of the cyclic iodocarbonate **74** was very scale dependent. Thus, strict TLC control was imperative in order to obtain reproducibly high yields and avoid further methoxide addition to epoxide **75**.

The elaboration of alcohol **75** to **64** required TBS protection under TBSCl/TMEDA conditions, followed by epoxide opening in **65** using sulfonium ylid generated *in situ* from Me₃SOTf and ⁿBuLi and afforded the C24-C30 fragment in 89% yield over 2 steps (Scheme 4.10.3).

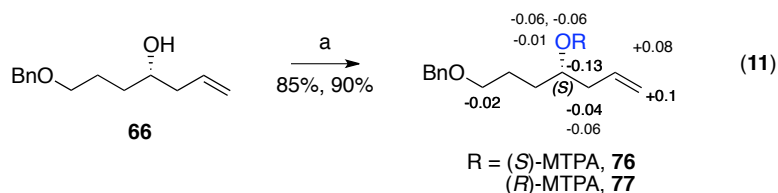
Scheme 4.10.3: Synthesis of the Allylic Alcohol **64**



Reaction conditions: a) TBSCl, TMEDA, DMF, RT, 97%. b) Me₃SOTf, ⁿBuLi, THF, -10 °C to 0 °C, 92%.

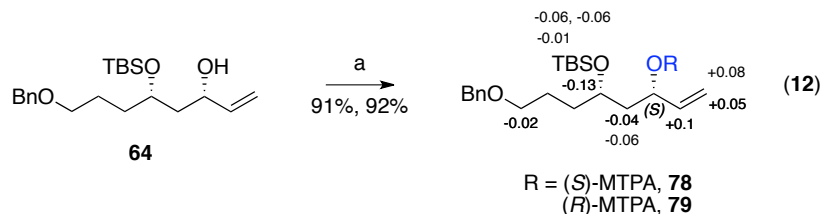
4.11 Stereochemistry Proof of Fragments **66** and **64**

The absolute configuration of the C27 stereocentre introduced by asymmetric allylation was confirmed by comparing the sign of the optical rotation of **66** with the known literature value for this compound, which suggested that (*S*)-homoallylic alcohol was formed. To gain further evidence, the modified Mosher esters analysis was carried out. The formation of MTPA esters from alcohol **66** and application of the Kakisawa conformational model¹⁰ unambiguously proved the (*S*)-configuration at C27 (eq. 11).



Reaction conditions: a) (*R*)-MTPA-Cl, *cat.* DMAP, Py, DCM, RT, 91%.
b) (*S*)-MTPA-Cl, *cat.* DMAP, Py, DCM, RT, 92%.

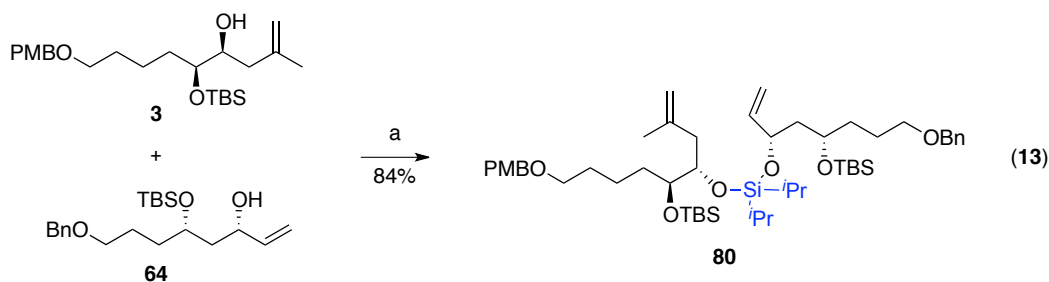
Similarly, the modified Mosher esters method was used to assign the (*S*) configuration of the C25 stereocentre (eq. 12). The latter was in accordance with the 1,3-*syn* stereinduction expected during the cyclic iodocarbonate formation step.



Reaction conditions: a) (*R*)-MTPA-Cl, *cat.* DMAP, Py, DCM, RT, 91%.
 b) (*S*)-MTPA-Cl, *cat.* DMAP, Py, DCM, RT, 92%.

4.12 Synthesis of Fragment 63

With substantial quantities of both metathesis precursors in hand, we moved towards the synthesis of the C15-C30 fragment. By employing the similar TST strategy described in Chapter 4.7, smooth formation of the mixed silaketal **80** was achieved in excellent yield by sequential reaction of alcohols **3** and **64** with $i\text{Pr}_2\text{SiCl}_2$ used as a temporary tether surrogate (eq. 13).



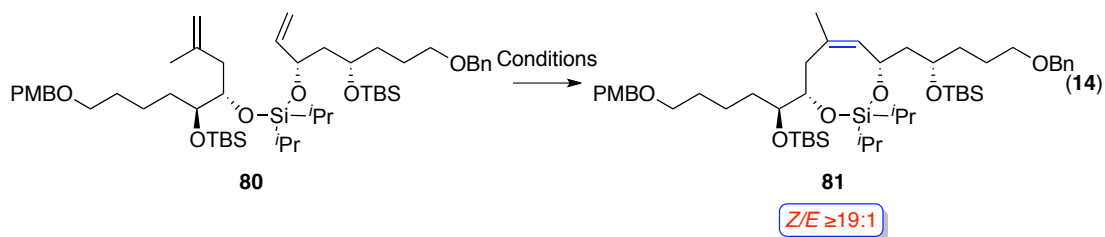
Reaction conditions: a) **3**, $i\text{Pr}_2\text{SiCl}_2$, imid, DCM, 0 °C to RT, then **64**, imid, DCM, 84%.

We then turned our attention to RCM reaction of **80**. The formation of cyclooctanoids from acyclic precursors is regarded to be the one of most challenging reactions due to the developing ring strain and restricted bond rotations in the precyclisation conformer.³² Additionally, the formation of trisubstituted olefins in the ring-closing act represents a significant challenge due to steric and

conformational effects within the molecule.³³ Subsequently, high catalyst loadings (up to 50 mol%), long reaction times and high temperatures are generally needed to pursue the product formation. Several strategies were developed to overcome the sluggishness of the process. These include, the introduction of a conformational constraint that favours the cyclisation^{32a} and the development of sterically less hindered Grubbs carbenes, by reducing the steric bulk of *N*-heterocyclic carbene ligands.³⁴

In studies carried out by Dr. Alen Cusak, no systematic research was carried out towards the optimisation of the RCM reaction for the formation of **53** and **56** based on the catalyst design, because of the scarce availability of ruthenium carbenes at that time. We anticipated that variations in catalyst (Figure 4.12.1), temperature and solvent could provide improvements in the efficiency of the transformation (Table 4.12.1). Initial reaction using standard conditions comprising of 30 mol% of G-II catalyst in refluxing DCM resulted in 96% conversion with 3% of dimeric materials (entry 1). Interestingly, application of the Fürstner's catalyst **74**³⁵ and the ruthenium carbene developed by Nolan *et al.* **75**³⁶ proved to be less efficient (entry 2 and 3). When the transformation was carried at higher temperature in DCE, the moderate conversion was observed with more dimers being formed (entry 4). In an attempt to increase an effective catalyst concentration, the syringe pump addition of the carbene was attempted. However, this resulted in lower conversion and formation of more dimeric materials (entry 5 and 7). Interestingly, the stepwise addition of the catalyst led to a sharp decrease in reactivity of the system (entry 6).

Table 4.12.1: *Optimisation of the TST-RCM Reaction of Silaketol 80 (eq. 14)*



Entry	Catalyst	Conditions (temp. °C, solvent)	Conc. (mM)	Time (h)	Conversion ^a
1	30 mol% G-II	40, DCM	10	72	96%, 3% of dimers
2	30 mol% of 74	40, DCM	10	“	12%, no dimers
3	30 mol% of 75	40, DCM	10	“	67%, no dimers
4	30 mol% G-II	80, DCE	10	“	65%, 11% of dimers
5	30 mol% of G-II ^b	80, PhMe	5	“	90%, 8.7% of dimers
6	30 mol% of G-II ^c	80, PhMe	5	“	14%, no dimers
7	30 mol% of G-II ^b	40, DCM	10	“	43%, <5% of dimers
8	30 mol% G-II ^d	40, DCM	10	“	15%, no dimers
9	30 mol% of G-II^c	40, DCM	10	“	99%, <5% of dimers

^aDiastereomeric ratio and conversion determined by 500 MHz ¹H NMR analysis of crude reaction mixtures. ^bSyringe pump addition of the catalyst over 12 hours. ^cStepwise addition of the catalyst, 2x15 mol% in 24 hour interval. ^d1 equiv. of *p*-benzoquinone used as an additive.

As shown by Grubbs *et al.*,³⁷ addition of benzophenone to the reaction can increase the half-life of the metathesis catalyst. Unfortunately, in our case this strategy led to the shut down of the transformation (entry 8). Ultimately, the best yield (97%) of the ring-closing product was obtained by running the reaction in DCM and employing a stepwise addition of Grubbs 2nd generation catalyst over 72 h (entry 9).

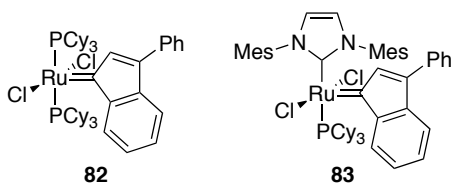
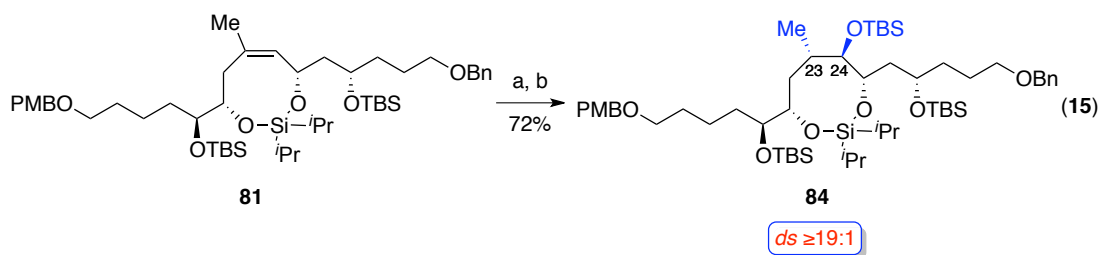


Figure 4.12.1: Structures of Ruthenium Carbenes **82** and **83**

With TST-RCM product in hand we carried out a hydroboration reaction to install the distinctive C23-C24 propionate stereocentres. Gratifyingly, application of the optimised hydroboration conditions (5 equiv. of $\text{BH}_3 \cdot \text{THF}$ at room temperature) resulted in formation of the desired **84** after silyl protection, in overall 72% yield (2 steps) with excellent diastereoselectivity ($ds \geq 19:1$) (eq. 15).



Reaction conditions: a) $\text{BH}_3 \cdot \text{THF}$, THF, RT, then H_2O_2 , NaOH, 0 °C to RT. b) TBSOTf, Et_3N , DCM, -78°C , $ds \geq 19:1$, 72% over 2 steps.

Unfortunately, hydroboration/oxidation conditions were not fully compatible with the substrate and one of the TBS ethers was cleaved during the reaction (based on ^1H NMR analysis of the crude reaction product), resulting in complex mixtures, thus preventing isolation of pure intermediate alcohol. Although the exact position of TBS cleavage was not clear, it seems reasonable that deprotection at C27 could arise from the *intramolecular* hydride transfer proceeding *via* a cyclic 6-membered transition state **85** (Figure 4.12.2).³⁸ Nevertheless, the two-step procedure for the synthesis of **84** proved to be an extremely convenient and reliable procedure even on a high scale.

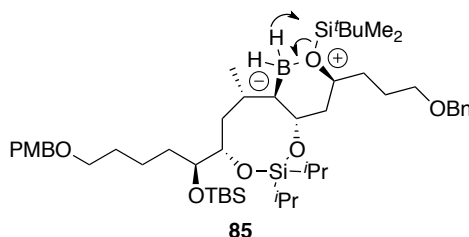


Figure 4.12.2: *Proposed Intramolecular Desilylation of 84*

The relative stereochemistry of the hydroboration product **84** was assigned using a series of 2D NOESY, HSQC, HMBC, COSY experiments in conjunction with coupling constant analysis (Figure 4.12.3). The observed spectroscopic data strongly suggested that *syn*-silaketal **84** adopted a boat-chair conformation.

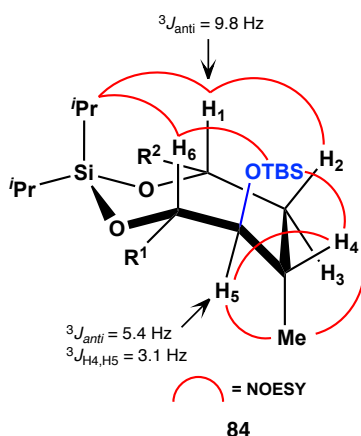


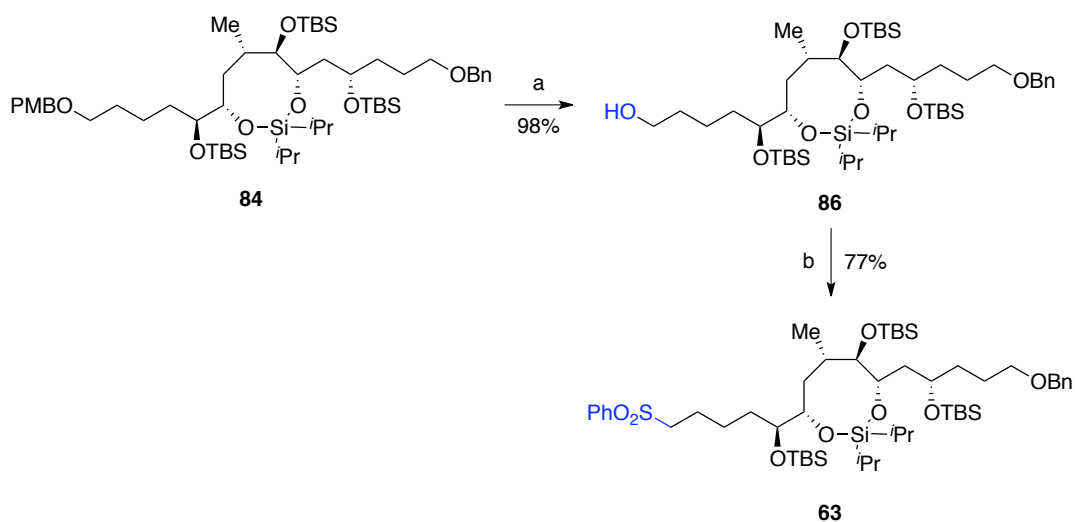
Figure 4.12.3: *Stereochemical Assignment of 84*

This spatial arrangement was supported by typical 1,2-diequatorial (*gauche*) coupling constant between H₅ and H₄ ($^3J_{\text{H}_4,\text{H}_5} = 3.1$ Hz) and nOe signals observed between H₂-H₁-*i*Pr-H₆-OTBS-H₄ residing on the same face of the molecule, in addition to the crucial enhancement between the pseudoequatorial protons H₄ and H₅. Furthermore, 1,2-diaxial coupling constants were observed, including $J_{\text{H}_1,\text{H}_3}$ (9.8 Hz) and $J_{\text{H}_5,\text{H}_6}$ (5.4 Hz). Although, the latter is smaller than common $^3J_{\text{anti}}$ coupling, this could be explained as a result of steric repulsion between R₁ and OTBS group leading to a narrowing of the dihedral angle between H₅ and H₆.

The proposed relative configuration of the hydroboration product was in full agreement with the model studies, which suggested the addition of the borane electrophile from the less sterically hindered face of the silyl ketal.² Notably, the conformational analysis of **84** using Spartan '08, calculated at a semi-empirical level of theory using an AM1 basis set, indicated a boat-chair as the lowest energy conformer, thus additionally supporting our elucidation.

The culmination of synthesis of the C16-C30 sulfone is outlined in Scheme 4.12.1. Chemoselective deprotection of the primary PMB ether using DDQ in buffered DCM afforded alcohol **86** in excellent yield. Conversion of **86** to sulfone **63** was achieved using Mitsunobu conditions,³⁹ employing PhSSPh and PBu₃, followed by a one-pot oxidation of the intermediate sulfide with hydrogen peroxide and ammonium molybdate complex.⁴⁰

Scheme 4.12.1: Synthesis of Sulfone 63



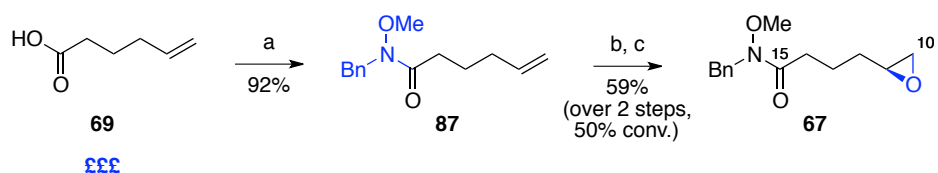
Reaction conditions: a) DDQ, DCM/pH 7 buffer (20:1), 0 °C to RT, 98%. b) PhSSPh, PBu₃, THF, then H₂O₂, cat. (NH₄)₆Mo₇O₂₄·4H₂O, 0 °C to RT, 77%.

4.13 Revised Synthesis of the C10-C15 Fragment

The revised synthesis of the C10-C15 fragment **67** began with construction of Weinreb amide using CDI coupling (Scheme 4.13.1). Activation of the

commercially available acid **70** via formation of imidazolide intermediate, followed by addition of *N*-benzyl-*N*-methoxyamine afforded **87** in excellent yield. Successive epoxidation was accomplished under biphasic conditions using *in situ* generated DMDO in 84% yield, whereas conventional epoxidation with *m*CPBA was not compatible with the amide and led to the decomposition. Finally, installation of the crucial C14 stereocentre in **67** was achieved using Jacobsen's hydrolytic kinetic resolution of the terminal epoxide in acceptable yield. The absolute configuration of epoxide **67** was assigned as (*S*) using the model for HKR discussed in Chapter 4.6.

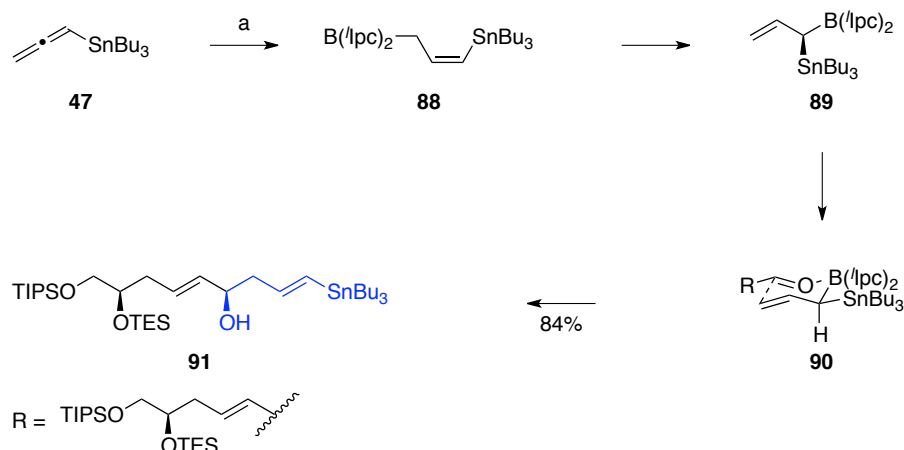
Scheme 4.13.1: Synthesis of Fragment 67



Reaction conditions: a) CDI, BnNH(OMe), DCM, 0 °C to RT, 92%. b) Acetone, Oxone®, NaHCO₃, EtOAc/H₂O (1:1), 98%. c) *cat.* (*S,S*)-OAc-**33**, H₂O, THF, 0 °C to RT, 60% (based on 50% conv.), >99% *ee*.

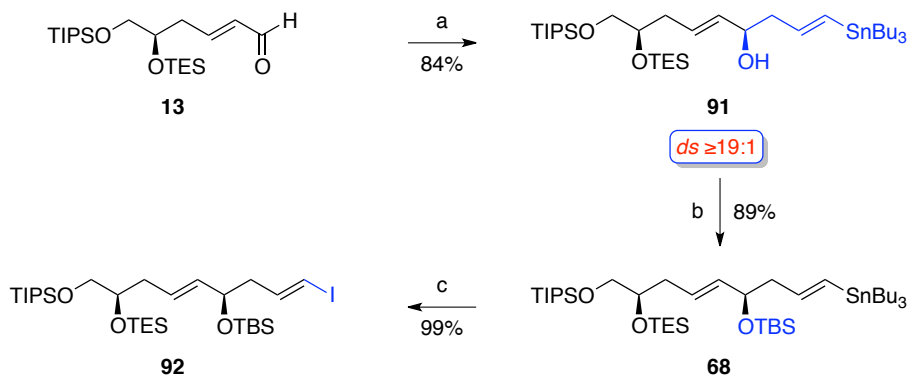
4.14 Revised Synthesis of the C1-C9 Fragment

For the preparation of the C1-C9 fragment we planned to implement the allylboration methodology developed by the Roush group.⁴¹ Generation of the chiral bimetallic derivative **88** by hydroboration of allenyl stannane **47** with (*ⁱ*Lpc)₂BH at −78 °C, followed by the thermodynamic 1,3-borotropic rearrangement at −20 °C gave the allyltin reagent **89** (Scheme 4.14.1). Addition of the α,β -unsaturated aldehyde **13** to **89** at −78 °C in Et₂O led to the homoallylic alcohol **91** with excellent stereocontrol (*ds* ≥ 19:1) after oxidative work-up. The stereochemical course of the process could be rationalised by invoking the chair-like cyclic transition state **90**, which effects the formation of C6-(*R*) and is consistent with the general sense of asymmetric induction by the -B(*ⁱ*Lpc)₂ unit in allylation and crotylation reactions.⁴²

Scheme 4.14.1: Allylboration of **13**

Reaction conditions: a) $(^t\text{Ipc})_2\text{BH}$, Et_2O , $-78\text{ }^\circ\text{C}$ to $-20\text{ }^\circ\text{C}$, then **13**, Et_2O , $-78\text{ }^\circ\text{C}$, 84%, $ds \geq 19:1$.

With successful implementation of the Roush allylboration the resulting secondary alcohol **91** was protected as TBS ether **68** (Scheme 4.14.2). Tin-iodine exchange in the latter afforded the vinyl iodide **92** as a Weinreb coupling precursor alternative to **68** (99% yield).

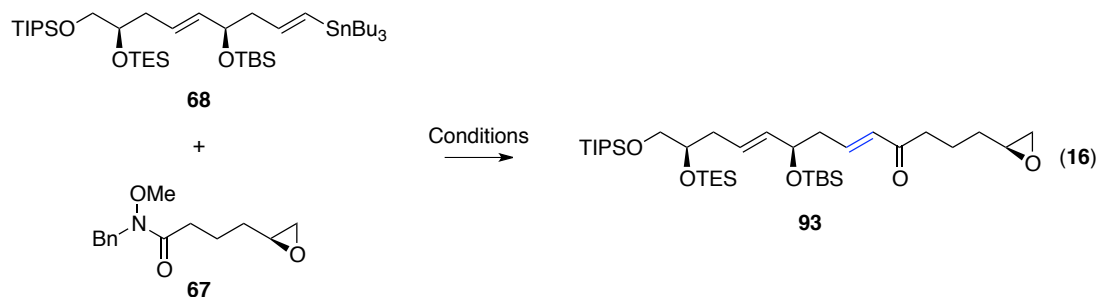
Scheme 4.14.2: Synthesis of the Vinyl Stannane **68 and Iodide **92****

Reaction conditions: a) **47**, $(^t\text{Ipc})_2\text{BH}$, Et_2O , $-78\text{ }^\circ\text{C}$ to $-20\text{ }^\circ\text{C}$, then **13**, Et_2O , $-78\text{ }^\circ\text{C}$, 89%, $ds \geq 19:1$. b) TBSOTf, Et_3N , DCM, $0\text{ }^\circ\text{C}$, 95%. c) I_2 , Et_2O , $0\text{ }^\circ\text{C}$, 99%.

4.15 Revised Synthesis of the C1-C15 Fragment

Initial attempts to achieve the C9-C10 bond formation by reaction of Weinreb amide **67** with the vinyl lithium reagent derived from stannane **68** were

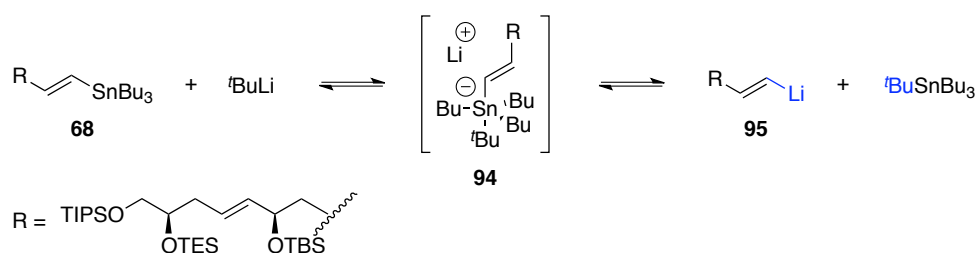
unsuccessful (eq. 16). We screened an array of bases including n BuLi, t BuLi, MeLi at different temperatures (0 °C to -78 °C) and solvents (THF, Et₂O), but none of the required product was obtained and only starting materials were recovered. Control experiments involving addition of base, followed by CD₃OD showed no deuterium incorporation in the quenched nucleophile.



Reaction conditions: RLi, Et₂O or THF, -78 °C to 0 °C

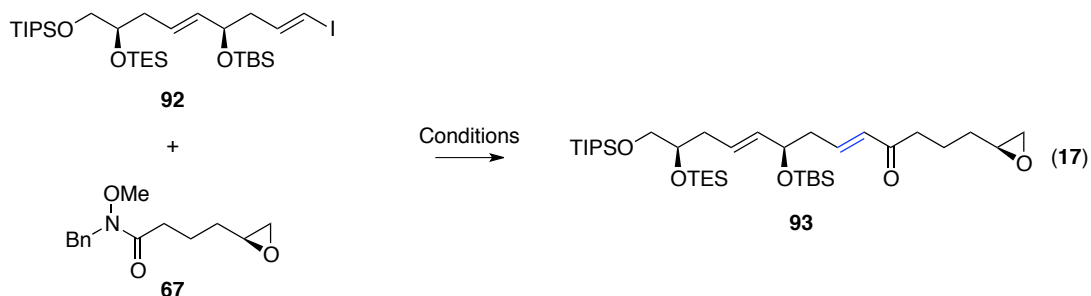
According to the literature, tin-lithium exchange is regarded as a reversible process and proceeds through the intermediacy of the pentacoordinated ‘ate’ complex, *e.g.* **94** (Scheme 4.15.3).⁴³ The position of the equilibrium is determined by the stability of the organolithium **95** and it is shifted towards products that deliver the best stabilisation of an anionic charge. However, in certain cases the ‘ate’ complex **94** is more stable than possible organolithium products and the exchange reaction does not occur. This could explain our inability to access the vinyl lithium **95** following the attempted transmetalation.

Scheme 4.15.3: *Tin-Lithium Exchange Mechanism*



In a search of possible coupling precursors we elected to exploit the halogen-lithium exchange as an appealing alternative to produce vinyl lithium species. The detailed results concerning Weinreb coupling of the vinyl lithium nucleophile derived from iodide **92** are presented in Table 4.15.1.

Table 4.15.1: *Optimisation of the Weinreb Coupling with Vinyl Iodide 92 (eq. 17)*



Entry	Conditions	Yield (%) ^a
1	<i>t</i> BuLi (2 equiv.), Et ₂ O, −78 °C	28
2	<i>n</i> BuLi (1 equiv.), Et ₂ O, −78 °C	30
3	<i>t</i> BuLi (2 equiv.), Et ₂ O/hexanes (5:1), −78 °C	24
4	<i>i</i> PrMgCl·LiCl, THF, −40 °C to 0 °C	n/r
5	<i>i</i>PrMgCl·LiCl, 15-Crown-5, THF, −10 °C	64

^aIsolated yield.

Initial attempts to achieve the pivotal coupling proceeded with moderate success. By conducting the exchange reaction with *t*BuLi in Et₂O at −78 °C, followed by addition of **67**, the incomplete conversion of the amide was observed even when excess of nucleophile was employed (up to 3 equiv.). Changing the base to less active *n*BuLi did not make much difference in terms of yield (entry 2). Further efforts to alleviate the reactivity of the system using hexane as co-solvent failed to improve the conversion of **92** into ketone **93** (entry 3).

To get some insight into the process, we performed the deuteration studies on iodide **92**. The ¹H NMR analysis of the crude CD₃OD quenched product showed

substantial amounts of the protonated nucleophile, which presumably arrived from a competitive reaction of the vinyl lithium intermediate with ^tBuI produced during the exchange. It is noteworthy that no Wurtz coupling products were observed. In an effort to optimise the reaction, the reversed addition of iodide **92** to a solution of ^tBuLi in Et₂O/hexanes was employed, which is known to reduce the undesired reaction with ^tBuI. Unfortunately, this attempt did not improve the formation of the desired product.

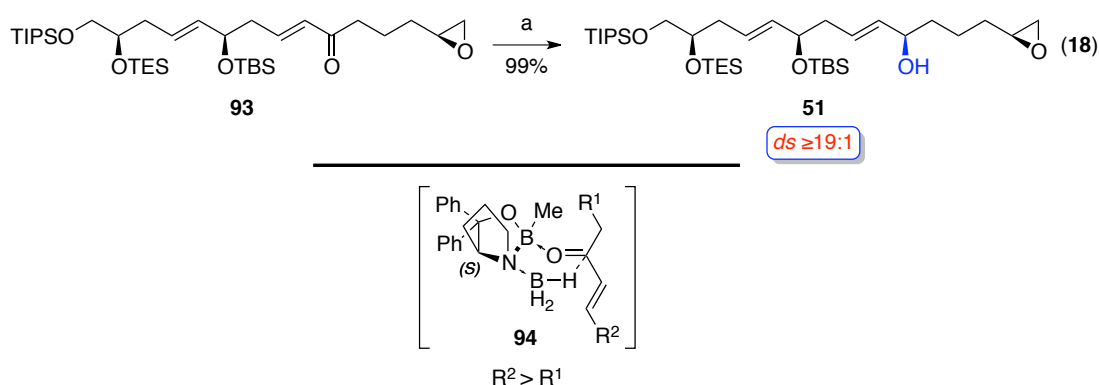
In search for an alternative preparation of vinyl metals, we turned our attention to the chemoselective ⁱPrMgCl·LiCl mediated iodine-magnesium exchange reaction of non-activated vinyl iodides developed by the Knochel's group.⁴⁴ We planned to take an advantage of the inherent inactivity of secondary Grignard reagents (*i.e.* ⁱPrMgCl) toward the Weinreb amides and achieve formation of vinyl magnesium adduct of **92**, which should then selectively add to **67**. Surprisingly, application of the reported Mg-I exchange conditions to iodide **92** led to absolutely no conversion and unchanged starting materials were recovered (entry 4). The exact reason for this was unclear, although model iodide halogen-magnesium exchange was shown to proceed, although with lower efficiency than was reported in the seminal publication.

In successive publications, Knochel and co-workers extended the exchange methodology to aromatic bromides and showed that a combination of ⁱPrMgCl·LiCl with chelating additives such as 15-crown-5 or 1,4-dioxane could improve the conversion of halogen-magnesium exchange by enforcement of an 'anionic Schlenk equilibrium'.⁴⁵ These advanced conditions were successfully applied by the Castle group for the union of a cyclic vinyl iodide and a Weinreb amide during the total

synthesis of (–)-acutumine.⁴⁶ Intrigued by these reports, we aimed to exploit new conditions for synthesis of **93**.

Initial results revealed good conversion of iodide **92**, but the yield of the desired coupling product was still low due to the incomplete consumption of amide **67**. After some experimentation, we discovered that by employing two equivalents of vinyl iodide, full conversion of **67** was observed and the enone **93** was obtained in an improved 64% yield (entry 5). It should be noted, that no vinyl addition to epoxide was observed in any of experiments. Whereas, the moderate yield of **93** could be partially explained by the epoxide opening with chloride anion proceeding as a major side reaction.

With a reliable route to the α,β -unsaturated ketone **93** available, we set out to introduce the C10 centre stereoselectively using CBS reduction (eq. 18).⁴⁷ Gratifyingly, treatment **93** with a stoichiometric amount of chiral Me-(*S*)-CBS reagent and excess $\text{BH}_3\cdot\text{DMS}$ at $-40\text{ }^\circ\text{C}$ afforded the required allylic alcohol **51** in excellent yield and with high stereocontrol ($ds \geq 19:1$).

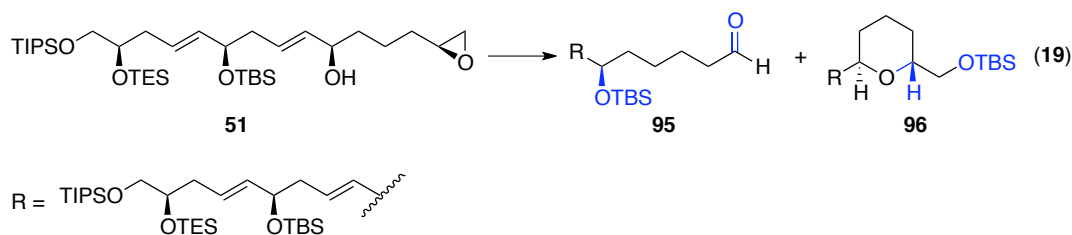


Reaction conditions: a) (*R*)-Me-CBS, $\text{BH}_3\cdot\text{DMS}$, THF, $-40\text{ }^\circ\text{C}$, 99%, $ds \geq 19:1$.

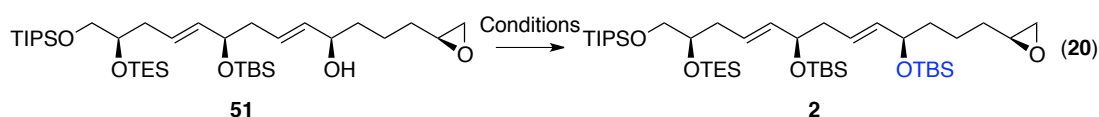
The selective formation of the (*R*)-configured allylic alcohol **51** could be explained by the formation of the cyclic boat-like transition state **94**, where the coordination of the Me-(*S*)-CBS-borane complex to the ketone at the sterically more

accessible lone pair results in the exclusive delivery of the hydride from the *Si*-face of the carbonyl group.

For the last step in the synthesis of the C1-C15 fragment, we planned to implement the earlier described protection of alcohol **51** using TBSOTf/Et₃N (Chapter 4.6). While this reaction was successfully carried out on a small scale, we found that the yield can dramatically decrease upon the scale up and had a strong dependence on the freshness of TBSOTf reagent used. Evaluation of side products suggested the decomposition of the epoxide moiety with the incorporation of one TBS ether moiety. We believed that reagent's residual triflic acid in the form of lutidinium salt or even TBSOTf itself can act as Lewis acid and induce Meinwald epoxide rearrangement and/or *intramolecular 6-exo-tet* cyclisation what undermines the effectiveness of the process and considerably reduces the yield (eq. 19).



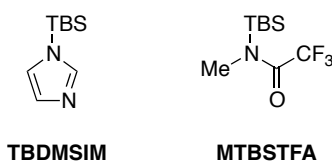
We screened a range of TBS protection conditions and were astonished to find that most silylation methods were absolutely incompatible with the 6-hydroxy epoxide system (eq. 20, Table 4.15.2). As mentioned above, TBSOTf addition at $-78\text{ }^\circ\text{C}$ afforded **2** with yields ranging between 35-97%, depending on the batch of the silylating reagent used (entry 1), whereas standard conditions, using TBSCl/imid in DMF led to decomposition only (entry 2).

Table 4.15.2: *Optimisation of the TBS Protection of 51 (eq. 20)*

Entry	Conditions	Yield (%) ^a
1	TBSOTf, 2,6-lutidine, DCM, -78 °C	35-97
2	TBSCl, imid, DMF, 0 °C	Decomp.
3	TBSCl, TMEDA, DCM, 0 °C	“
4	TBSCl, Li ₂ S, DMF, 0 °C	“
5	TBDMSIM, DMAP, MeCN, RT	50 (95 b.r.s.m)
6	MTBSTFA, DMAP, MeCN, RT	Quant.

^aIsolated yield.

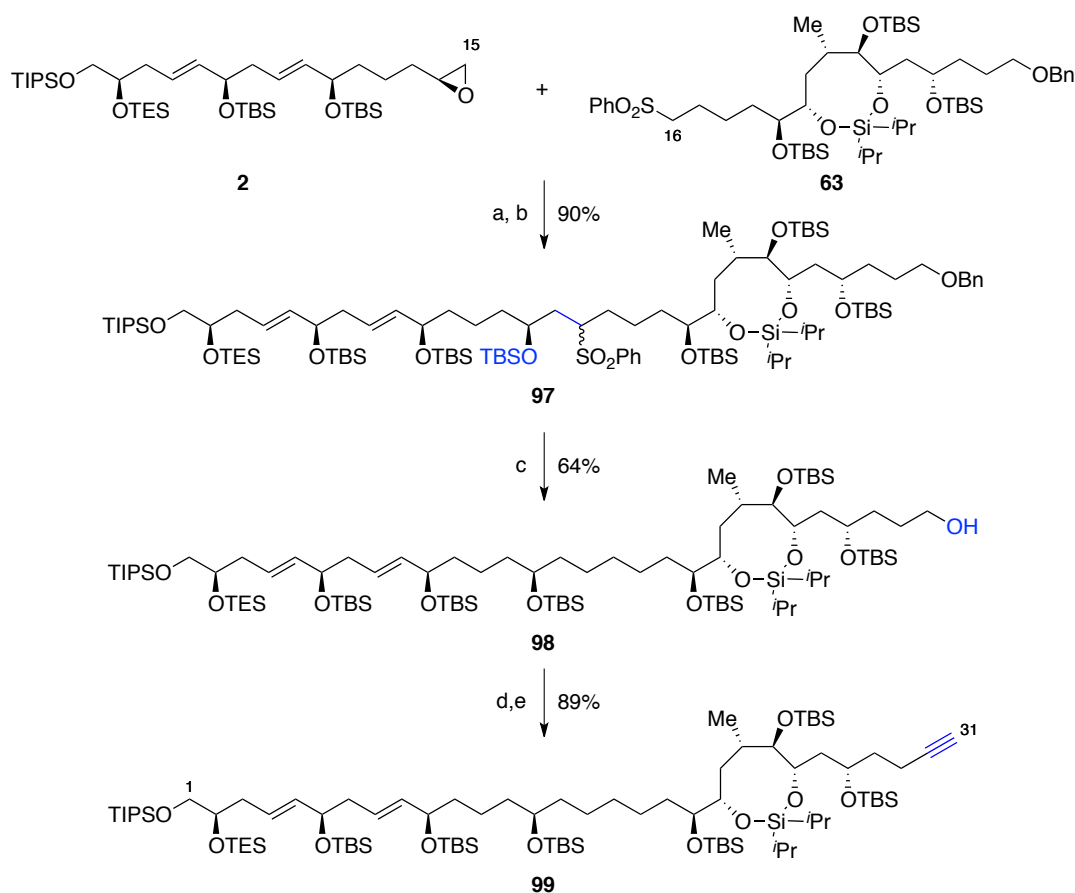
Application of the procedure, which was found effective for the protection of hydroxyepoxide **75**, gave an unacceptable outcome as well (entry 3). We tried silylation using mildly acidic TBSCl/Li₂S system, however no product was obtained (entry 4). We reasoned that protection under neutral conditions that avoid formation of Lewis acids could obviate the activation and decomposition of the epoxide in **51**. Gratifyingly, reaction with neutral TBDMSIM reagent (Figure 4.15.1) at elevated temperature afforded the desired **2** in 50% yield (95% b.r.s.m.) with imidazole as the only side product (entry 5). Ultimately, substitution of TBS donor with the more reactive MTBSTFA led to quantitative formation of **2** in just 3 h at room temperature (entry 6). Having developed a sequence to access two major fragments we could move to the pivotal coupling and to forge the key C15-C16 bond.

**Figure 4.15.1:** *Neutral Silylating Reagents*

4.16 Completion of the C1-C31 fragment of Amphidinol 3

Following our initial plan, epoxide opening was achieved by the lithiation of two equivalents of sulfone **63** with $n\text{BuLi}$, followed by addition of **2** and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at -78°C to furnish the desired β -hydroxysulfone product (Scheme 4.16.1). Due to the similar R_f values of the addition product and sulfone **63**, the crude reaction mixture was used directly in the following silylation with TBSOTf and afforded the C15-C16 coupling product **97** as a mixture of inconsequential diastereoisomers at C16 in excellent overall yield (90%). At this stage, the dramatic difference in polarity of **97** and **63** accounted for the efficient recovery of the unreacted **63** (87% of sulfone recovered).

Scheme 4.16.1: Completion of the C1-C31 Fragment of Amphidinol 3



Reaction conditions: a) **63**, $n\text{BuLi}$, THF, -78°C , then **2**, $\text{BF}_3 \cdot \text{Et}_2\text{O}$. b) TBSOTf, Et_3N , DCM, 0°C , 90% over 2 steps. c) LiDBB, THF, -78°C , 64%. d) NMO, TPAP, DCM, 0°C , e) $\text{Me}(\text{CO})\text{C}(\text{N}_2)\text{P}(\text{O})(\text{OMe})_2$, K_2CO_3 , THF/MeOH (1:1), 0°C to RT, 89% over 2 steps.

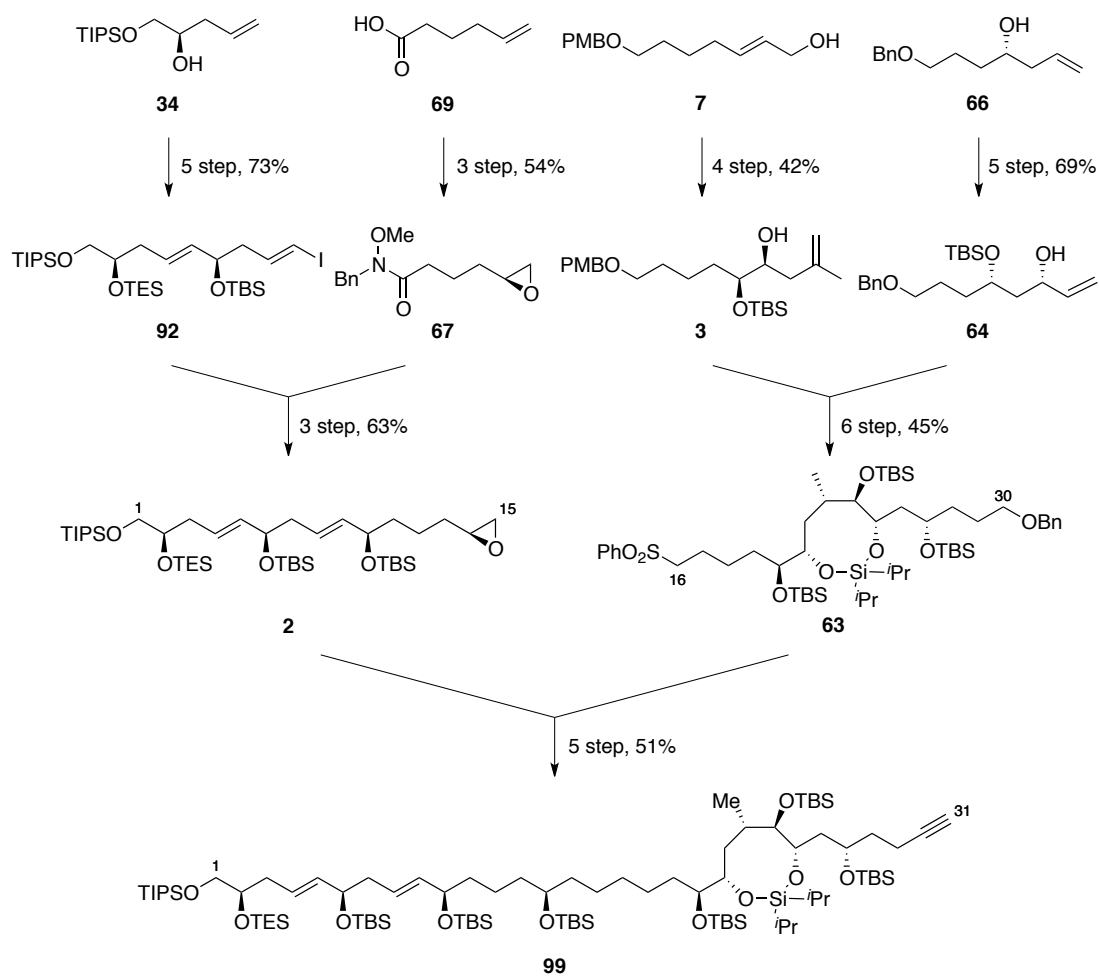
Next, we planned to employ single-electron reduction using lithium naphthalenide or di-*tert*-butylbiphenylide complex for the concomitant removal of the sulfone and cleavage of the primary benzyl ether moieties. Gratifyingly, addition of the freshly made LiDBB reagent (6 equiv.) to sulfone **97** at $-78\text{ }^{\circ}\text{C}$ in THF afforded the desired alcohol **98** in 64% yield. Oxidation of the latter using Ley's conditions (TPAP, NMO) and Seyferth–Gilbert homologation²⁹ of the intermediate aldehyde with Bestmann–Ohira reagent furnished alkyne **2**, which constitutes the C1-C31 fragment of amphidinol 3 (89% yield over 2 steps).

4.17 Conclusion

In the course of the synthetic studies a highly convergent enantioselective synthesis of the C1-C31 fragment of amphidinol 3 was developed (Scheme 4.17.1). Our route featured a rapid and easily scalable preparation of four structural units of similar complexity in 3 to 5 longest linear steps starting from known materials. Subsequent coupling of these fragments allowed for the expeditious increase in complexity and afforded two major C1-C15 and C16-C30 segments of AM3. It is worth mentioning, that application of the recently developed TST-RCM-based hydroboration reaction permitted the highly stereoselective installation of the pivotal C23-C24 propionate unit solely based on the substrate control. The smooth coupling of two fragments was then achieved by regioselective addition of a sulfonyl anion to the epoxide and was followed by the reductive removal of the sulfone moiety and the C30 masking group in one-pot. Ensuing oxidation/homologation furnished the C1-C31 alkyne and completed the synthesis of the polyol fragment of amphidinol 3 in 16 steps (longest linear sequence) with 15.9% overall yield corresponding to an average yield of 89.1% per step. Finally, we envisage that the latter alkyne could be easily

elaborated in future studies towards the crucial coupling with the C32-C52 *bis*-THP segment of the natural product.

Scheme 4.17.1: Overview of the Synthesis of the C1-C31 Fragment of Amphidinol 3



4.18 Experimental Part. General Information

All reactions were carried out under Argon atmosphere, unless otherwise stated. Anhydrous DCM, hexane, Et₂O were obtained by passing degassed solvents through activated alumina columns in a Grubbs solvent purification system (*PureSolv MD-6* of *Innovative Technology Inc.*). Anhydrous THF was obtained by distillation from benzophenone ketyl. Anhydrous MeOH, DMF and MeCN were purchased from *Aldrich*. 2,6-Lutidine, Et₃N, BF₃·Et₂O were distilled from CaH₂ under nitrogen and stored under 4 Å MS. Anhydrous K₂CO₃ dried at 100 °C for 16 hours *in vacuo*. For other general information, see Chapter 2.

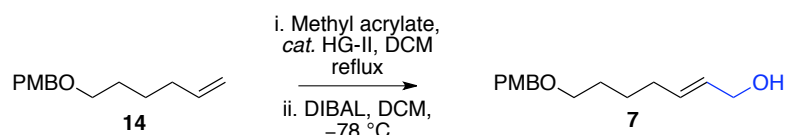
1-((Hex-5-en-1-yloxy)methyl)-4-methoxybenzene (14)³

To a cooled to 0 °C suspension of sodium hydride (3.60 g, 60% in mineral oil, 90 mmol) in DMF (120 mL) was added 5-hexen-1-ol (**12**) (6.01 g, 60 mmol), followed by 4-methoxybenzylchloride (11.4 mL, 84 mmol). The solution warmed to room temperature and stirred for *ca.* 18 h (TLC control). The reaction mixture was cooled to 0 °C, quenched with saturated aqueous NH₄Cl and partitioned between Et₂O and water. Layers were separated and the aqueous phase was washed with Et₂O (2x). The combined organic layers were washed with 1 N aqueous HCl, saturated aqueous NaHCO₃, brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et₂O/hexanes – 1:22, 1:20) afforded the *p*-methoxybenzyl ether **14** (13.2 g, 59.9 mmol, 100% yield) as a colourless oil.

R_f = 0.7 (Et₂O/hexanes – 1:1)

^1H NMR (500 MHz, CDCl_3) δ 7.27-7.25 (m, 2H), 6.89-6.87 (m, 2H), 5.80 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H), 5.00 (dd, J = 17.2, 1.4 Hz, 1H), 4.94 (dq, J = 10.1, 0.9 Hz, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.44 (t, J = 6.6 Hz, 2H), 2.06 (q, J = 7.2 Hz, 2H), 1.62 (app. dt, A of A_2BX_2 , J_{AB} = 14.6 Hz, J_{AX} = 7.1 Hz, 2H), 1.46 (app. dt, B of ABX_2 , J_{AB} = 15.1 Hz, J_{BX} = 7.6 Hz, 1H), 1.45 (app. dt, B of ABX_2 , J_{AB} = 15.1 Hz, J_{BX} = 7.6 Hz, 1H).

IR (Neat) 2931 (w), 2854 (w), 1640 (w), 1612 (w), 1512 (s), 1099 (m) cm^{-1} .



(*E*)-7-((4-Methoxybenzyl)oxy)hept-2-en-1-ol (7)⁶

To a solution of **14** (13.22 g, 60 mmol) and methyl acrylate (27.0 mL, 300 mmol) in DCM (150 mL) was added Hoveyda-Grubbs 2nd generation catalyst (0.327 g, 0.522 mmol). The reaction mixture was refluxed for *ca.* 2 h (TLC control), before it was concentrated *in vacuo* and the crude ester intermediate was dissolved in DCM (150 mL). The solution was cooled to $-78\text{ }^{\circ}\text{C}$ and treated with DIBAL-H (198 mL, 1 M in hexanes, 198 mmol). The reaction mixture was stirred for *ca.* 15 min (TLC control), then quenched with MeOH (5 mL) and diluted with EtOAc and saturated aqueous Rochelle salt. The vigorously stirred mixture was left to warm up to room temperature overnight. After *ca.* 15 h phases were separated and the aqueous layer was washed with EtOAc (4x). The combined organic phases were washed with brine. The aqueous phases were back extracted with EtOAc. The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /petroleum ether – 1:1, 1.25:1) afforded the allylic alcohol **7** (14.35 g, 57.20 mmol, 95% yield) as a colourless oil.

$R_f = 0.16$ (Et₂O/hexanes – 1:1)

¹H NMR (500 MHz, CDCl₃) δ 7.27-7.24 (m, 2H), 6.89-6.86 (m, 2H), 5.71-5.60 (m, 2H), 4.43 (s, 2H), 4.08 (d, $J = 5.1$ Hz, 2H), 3.80 (s, 3H), 3.44 (t, $J = 6.5$ Hz, 2H), 2.06 (q, $J = 6.9$ Hz, 2H), 1.61 (app. dt, $J = 14.6, 6.7$ Hz, 2H), 1.57 (br s, 1H), 1.46 (app. dt, $J = 14.7, 7.3$ Hz, 2H).

IR (Neat) 3388 (br), 2933 (m), 2857 (m), 1670 (w), 1612 (m), 1512 (s), 1089 (m) cm⁻¹.



(E)-1-(((7-Bromohept-5-en-1-yl)oxy)methyl)-4-methoxybenzene (17)

To a cooled to 0 °C solution of imidazole (15.0 g, 221 mmol) and triphenylphosphine (38.3 g, 146 mmol) in DCM (210 mL) was carefully added bromine (7.4 mL, 143 mmol) dropwise. The resultant yellow slurry was stirred for *ca.* 15 min and then a solution of **7** (14.35 g, 57.3 mmol) and 2-methylbut-2-ene (20 mL, 57.3 mmol) in DCM (50 mL) was added dropwise. After *ca.* 15 min (TLC control) the reaction was quenched by addition of MeOH (1 mL), diluted with petroleum ether and filtered through a large pad of silica gel (washed with Et₂O/petroleum ether – 1:5). Concentration *in vacuo* afforded the crude allylic bromide **17**, which was used in the following step without purification.

An analytical sample was obtained by purification using flash chromatography (silica gel, Et₂O/hexanes – 1:15) as a colourless oil.

$R_f = 0.65$ (Et₂O/hexanes – 1:1).

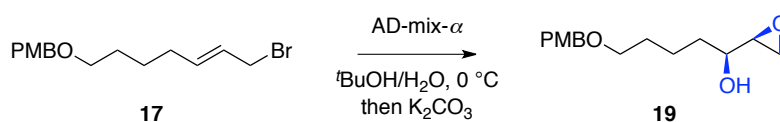
¹H NMR (500 MHz, CDCl₃) δ 7.27-7.25 (m, 2H), 6.90-6.87 (m, 2H), 5.76 (dt, $J = 15.0, 6.6$ Hz, 1H), 5.68 (dt, $J = 15.0, 7.5$ Hz, 1H), 4.43 (s, 2H), 3.95 (d, $J = 7.3$ Hz,

2H), 3.80 (s, 3H), 3.43 (t, $J = 6.5$ Hz, 2H), 2.07 (q, $J = 7.1$ Hz, 2H), 1.60 (app. dt, A of A_2BX_2 , $J_{AB} = 14.5$ Hz, $J_{AX} = 7.1$ Hz, 2H), 1.46 (app. dt, B of AB_2X_2 , $J_{AB} = 15.0$ Hz, $J_{BX} = 7.5$ Hz, 2H).

^{13}C NMR (125 MHz, CDCl_3) δ 159.16 (e), 136.46 (o), 130.69 (e), 129.39 (o), 126.62 (o), 113.82 (o), 72.66 (e), 69.87 (e), 55.39 (o), 33.82 (e), 31.97 (e), 29.31 (e), 25.54 (e).

IR (Neat) 2999 (w), 2933 (m), 2855 (m), 1660 (w), 1612 (m), 1586 (w), 1512 (s), 1098 (s), 757 (w) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{15}\text{H}_{21}\text{O}_2\text{Na}^{79}\text{Br}$ 335.0623, found 335.0611, calcd for $\text{C}_{15}\text{H}_{21}\text{O}_2\text{Na}^{81}\text{Br}$ 337.0602, found 337.0618.



(S)-5-((4-Methoxybenzyl)oxy)-1-((S)-oxiran-2-yl)pentan-1-ol (19)

To a cooled to 0 °C solution of crude **17** (~57.3 mmol) in a 1:1 mixture of $t\text{BuOH}$ and water (560 mL) was added a mixture of potassium osmate(IV) dihydrate (0.211 g, 0.573 mmol), methanesulfonamide (5.45 g, 57.3 mmol), K_2CO_3 (23.76 g, 172 mmol), $\text{K}_3[\text{Fe}(\text{CN})_6]$ (56.6 g, 172 mmol), $(\text{DHQ})_2\text{PHAL}$ (0.893 g, 1.146 mmol) and the reaction mixture was stirred at that temp for *ca.* 6 h (TLC control). Upon the consumption of the starting material, 39.6 g of K_2CO_3 and 100 mL of water were added and the reaction mixture was warmed to room temperature. The bromohydrine cyclisation progress was periodically checked by ^1H NMR of the reaction aliquots. After *ca.* 16 h the reaction mixture was quenched with 10 g of Na_2SO_3 and stirred for *ca.* 1 h. The resulted green solution was partitioned between water and EtOAc. Phases were separated and the aqueous layer was washed with

EtOAc (3x). The combined organic layers were washed with 2 N aqueous NaOH, brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et₂O/petroleum ether – 2.5:1) afforded the hydroxy epoxide **19** (11.5 g, 43.2 mmol, 75% yield) as a colourless oil.

R_f = 0.07 (Et₂O/hexanes – 1:1).

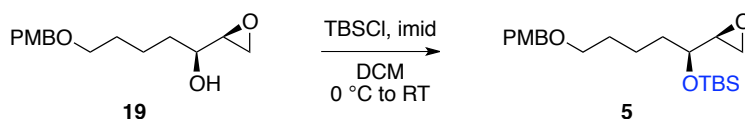
$[\alpha]_{\text{D}}^{20} +2.6$ (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.26-7.24 (m, 2H), 6.88-6.85 (m, 2H), 4.42 (s, 2H), 3.79 (s, 3H), 3.45 (t, *J* = 6.4 Hz, 2H), 3.41 (app. dt, *J* = 12.2, 6.1 Hz, 1H), 2.96 (ddd, *J* = 5.0, 4.0, 3.1 Hz, 1H), 2.80 (dd, A of AMX, *J*_{AM} = 4.8 Hz, *J*_{AX} = 4.7 Hz, 1H), 2.69 (dd, M of AMX, *J*_{AM} = 4.9 Hz, *J*_{MX} = 2.8 Hz, 1H), 2.04 (br s, 1H), 1.70-1.42 (m, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 159.14 (e), 130.63 (e), 129.27 (o), 113.77 (o), 72.59 (e), 71.60 (o), 69.80 (e), 55.35 (o), 55.28 (o), 45.16 (e), 34.14 (e), 29.65 (e), 22.09 (e).

IR (Neat) 3434 (w), 2936 (w), 2860 (w), 1612 (m), 1612 (w), 1512 (s), 1092 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₁₅H₂₂O₄Na 289.1416, found 289.1403.



***tert*-Butyl(((*S*)-5-((4-methoxybenzyl)oxy)-1-((*S*)-oxiran-2-yl)pentyl)oxy)dimethylsilane (**5**)**

A solution of **19** (2.8 g, 10.51 mmol) in DMF (30 mL) was treated with imidazole (2.15 g, 31.5 mmol) and TBSCl (3.17 g, 21.03 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for *ca.* 16 h (TLC control), then quenched with saturated aqueous NH₄Cl and partitioned between water and Et₂O.

Phases were separated and the aqueous layer was washed with Et₂O (2x). The combined organic layers were washed with water, brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et₂O/petroleum ether – 1:7, 1:6) afforded the TBS ether **5** (3.22 g, 8.46 mmol, 80% yield) as a colourless oil.

R_f = 0.6 (Et₂O/hexanes – 1:1).

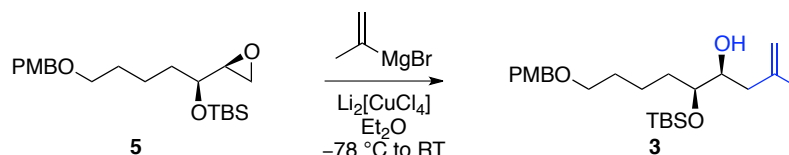
$[\alpha]_{\text{D}}^{20}$ –4.2 (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.26-7.24 (m, 2H), 6.89-6.86 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.44 (t, *J* = 6.5 Hz, 2H), 3.25 (app. td, *J* = 7.0, 4.8 Hz, 1H), 2.91 (ddd, *J* = 6.7, 4.0, 2.8 Hz, 1H), 2.77 (t, A of AX₂, *J*_{AX} = 4.5 Hz, 1H), 2.53 (dd, M of AMX, *J*_{AM} = 4.9 Hz, *J*_{MX} = 2.7 Hz, 1H), 1.65-1.35 (m, 6H), 0.91 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 159.13 (e), 130.70 (e), 129.23 (o), 113.76 (o), 74.58 (o), 72.58 (e), 69.87 (e), 55.95 (o), 55.27 (o), 44.91 (e), 34.57 (e), 29.80 (e), 25.90 (o), 22.07 (e), 18.20 (e), –4.34 (o), –4.97 (o).

IR (Neat) 2929 (w), 2856 (w), 1613 (w), 1513 (m), 1098 (s) cm^{–1}.

HRMS (ESI, [M+Na]⁺) calcd for C₂₁H₃₆O₄NaSi 403.2281, found 403.2296.



(4*S*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-9-((4-methoxybenzyl)oxy)-2-methylnon-1-en-4-ol (3**)**

Isopropenylmagnesium bromide (109 mL, 0.5 M in THF, 54.5 mmol) was diluted with Et₂O (120 mL) and the solution was cooled to –78 °C. Dilithium tetrachlorocuprate(II) (18.1 mL, 0.1 M in THF, 1.81 mmol) was added dropwise and

the resultant orange suspension was stirred at that temperature for *ca.* 10 min, followed by the addition of **5** (6.893 g, 18.11 mmol) in Et₂O (25 mL, with washings). The reaction mixture was left to slowly warm up to room temperature and stirred for *ca.* 14 h (TLC control), then quenched with a 4:1 mixture of saturated aqueous NH₄Cl and aqueous NH₄OH. The resultant mixture was partitioned between water and Et₂O. Phases were separated and the aqueous layer was washed with Et₂O (2x). The combined organic layers were washed with water, brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et₂O/petroleum ether – 1:4) afforded the homoallylic alcohol **3** (7.6 g, 17.98 mmol, 99% yield) as a colourless oil. The enantiomeric purity of **3** was determined by the formation of Mosher esters **20** and **21** and was shown to be 92% *ee*.

R_f = 0.58 (Et₂O/hexanes – 1:1).

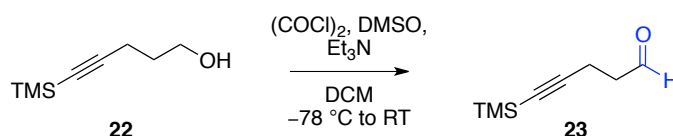
$[\alpha]_{\text{D}}^{20}$ –1.0 (*c* 0.5, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.27-7.25 (m, 2H), 6.88-6.86 (m, 2H), 4.84 (s, 1H), 4.77 (s, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.66 (app. dt, A of ABX₂, J_{AB} = 8.3 Hz, J_{AX} = 4.1 Hz, 1H), 3.59 (app. dt, B of ABX₂, J_{AB} = 5.5 Hz, J_{BX} = 3.4 Hz, 1H), 3.45 (app. dt, A of ABX₂, J_{AB} = 9.7 Hz, J_{AX} = 6.6 Hz, 1H), 3.43 (app. dt, B of ABX₂, J_{AB} = 9.7 Hz, J_{BX} = 6.6 Hz, 1H), 2.18 (dd, A of ABX, J_{AB} = 14.3 Hz, J_{AX} = 5.1 Hz, 1H), 2.16 (s, 1H), 2.14 (dd, B of ABX, J_{AB} = 14.0 Hz, J_{BX} = 8.6 Hz, 1H), 1.76 (s, 3H), 1.69-1.58 (m, 3H), 1.46-1.36 (m, 3H), 0.91 (s, 9H), 0.08 (s, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 159.12 (e), 142.99 (e), 130.70 (e), 129.23 (o), 113.75 (o), 112.70 (e), 74.46 (o), 72.56 (e), 70.38 (o), 69.92 (e), 55.26 (o), 42.09 (e), 33.21 (e), 29.98 (e), 25.93 (o), 22.52 (o), 22.03 (e), 18.13 (e), –4.09 (o), –4.50 (o).

IR (Neat) 3472 (br), 2930 (m), 2856 (m), 1647 (w), 1613 (w), 1512 (m), 1096 (m) cm^{–1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{24}H_{42}O_4NaSi$ 445.2750, found 445.2759.



5-(Trimethylsilyl)pent-4-ynal (**23**)¹³

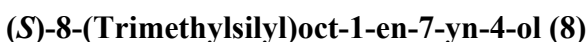
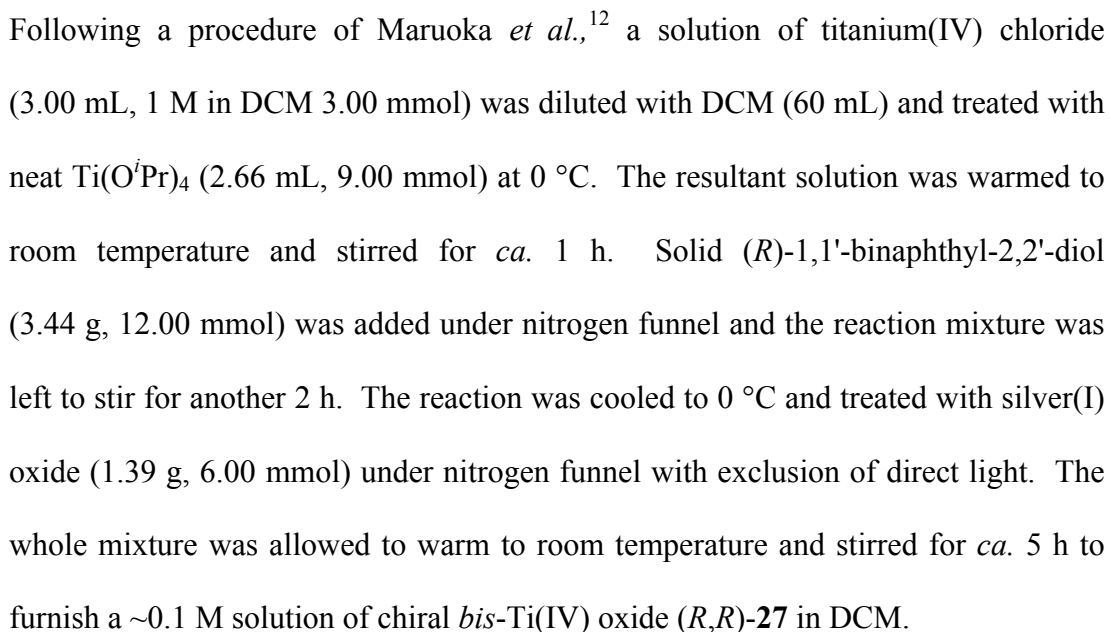
To a solution of oxalyl dichloride (2.68 mL, 31.2 mmol) in DCM (40 mL) at $-78\text{ }^{\circ}\text{C}$ was added DMSO (4.43 mL, 62.3 mmol) dropwise. After *ca.* 15 min a solution of 5-(trimethylsilyl)pent-4-yn-1-ol (**22**) (2.26 mL, 12.47 mmol) in DCM (30 mL with washings) was added and the mixture was stirred for *ca.* 20 min at $-78\text{ }^{\circ}\text{C}$ and *ca.* 50 min at $-40\text{ }^{\circ}\text{C}$. The reaction was cooled back to $-78\text{ }^{\circ}\text{C}$, treated with Et_3N (17.4 mL, 125 mmol) and then let to warm to room temperature. The mixture was quenched with saturated aqueous NH_4Cl and partitioned between water and Et_2O . Phases were separated and the aqueous layer was washed with Et_2O (2x). The combined organic layers were dried ($MgSO_4$), filtered and carefully concentrated at 250 Torr to afford crude volatile aldehyde **23** (1.77 g, 11.50 mmol, 92% yield), which was used in the following step without purification.

An analytical sample was obtained by purification using flash chromatography (silica gel, Et_2O /hexanes – 1:20, 1:15, 1:12) as a colourless oil.

$R_f = 0.48$ (Et_2O /hexanes – 1:2.5).

1H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 2.66 (t, A of A_2X_2 , $J_{AX} = 7.2$ Hz, 2H), 2.53 (t, X of A_2X_2 , $J_{AX} = 7.2$ Hz, 2H), 0.13 (s, 9H).

IR (Neat) 2931 (w), 2859 (w), 2722(w), 1721 (s) cm^{-1} .



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chromatography (silica gel, Et₂O/petroleum ether – 1:5, 1:4) afforded the homoallylic alcohol **8** (2.29 g, 11.64 mmol, 93% yield over 2 steps) as a colourless oil.

Enantiomeric excess of **8** was determined by chiral HPLC analysis of Bz ester and was shown to be 92-96% *ee*. Chiral AD-H column, IPA/Hex – 0.4:99.6, 0.3 mL/min, 25 °C, 210 nm, *t_r*(minor) = 16.3 min, *t_r* (major) = 17.5 min.

R_f = 0.42 (Et₂O/hexanes – 1:2.5).

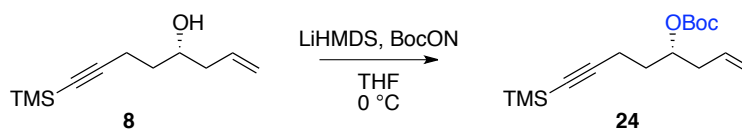
$[\alpha]_{\text{D}}^{20}$ –15.1 (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 5.83 (dddd, *J* = 16.2, 12.3, 9.7, 7.7, 6.7 Hz, 1H), 5.16-5.12 (m, 2H), 3.79 (octet, *J* = 4.1 Hz, 1H), 2.38 (t, *J* = 7.1 Hz, 2H), 2.31 (app. dddt, A of ABXYZ₂, *J_{AB}* = 13.9 Hz, *J_{AX}* = 6.4 Hz, *J_{AY}* = 4.9 Hz, *J_{AZ}* = 1.4 Hz, 1H), 2.20 (app. ddt, B of ABXY₂, *J_{AB}* = 14.1 Hz, *J_{BX}* = 7.6 Hz, *J_{BY}* = 1.0 Hz, 1H), 1.94 (d, *J* = 4.0 Hz, 1H), 1.71 (app. dtd, A of ABX₂Y, *J_{AB}* = 14.1 Hz, *J_{AX}* = 7.1 Hz, *J_{AY}* = 3.8 Hz, 1H), 1.65 (app. dtd, B of ABX₂Y, *J_{AB}* = 15.4 Hz, *J_{BX}* = 8.7 Hz, *J_{BY}* = 1.7 Hz, 1H), 0.14 (app. td, *J* = 3.5, 0.4 Hz, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 134.64 (o), 118.36 (e), 107.04 (e), 85.42 (e), 70.11 (o), 41.91 (e), 35.31 (e), 16.68 (e), 0.23 (o).

IR (Neat) 3348 (br), 3078 (w), 2958 (w), 2174 (w), 1642 (w), 1249 (m), 1062 (w) cm⁻¹.

HRMS (CI, [M+NH₄]⁺) calcd for C₁₁H₂₄NOSi 214.1627, found 214.1630.



(*S*)-*tert*-Butyl (8-(trimethylsilyl)oct-1-en-7-yn-4-yl) carbonate (24**)**

To a cooled to 0 °C solution of **8** (2.20 g, 11.21 mmol) in THF (30 mL) was added LiHMDS (14.6 mL, 1 M in THF, 14.6 mmol) dropwise. The reaction mixture stirred for *ca.* 10 min and treated with a solution of BocON (3.87 g, 15.70 mmol) in THF (4.5 mL with washings). After *ca.* 15 min (TLC control) the reaction mixture was quenched with saturated aqueous NH₄Cl and partitioned between water and DCM. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et₂O/petroleum ether – 2%) afforded carbonate **24** (3.17 g, 10.70 mmol, 95% yield) as a colourless oil.

R_f = 0.81 (Et₂O/hexanes – 1:1).

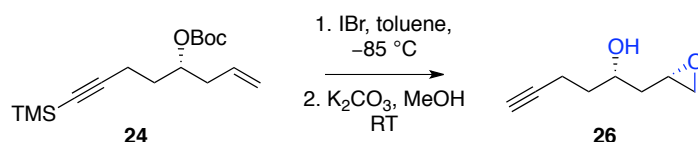
$[\alpha]_{\text{D}}^{20}$ –33.4 (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 5.77 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 5.11 (dd, *J* = 18.5, 1.4 Hz, 1H), 5.08 (dd, *J* = 11.2, 0.9 Hz, 1H), 4.76 (quintet, *J* = 6.3 Hz, 1H), 2.37 (t, *J* = 6.7 Hz, 2H), 2.31 (app. dt, A of ABX₂, *J*_{AB} = 17.1 Hz, *J*_{AX} = 7.4 Hz, 1H), 2.29 (app. ddt, B of ABXY₂, *J*_{AB} = 17.2 Hz, *J*_{BX} = 7.7 Hz, 1H), 1.81 (q, *J* = 7.1 Hz, 2H), 1.47 (s, 9H), 0.14 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ 153.26 (e), 133.30 (o), 118.26 (e), 106.18 (e), 85.18 (e), 82.04 (e), 75.43 (o), 38.63 (e), 32.64 (e), 27.92 (o), 16.29 (e), 0.22 (o).

IR (Neat) 2961 (w), 2177 (w), 1738 (s), 1643 (w), 1275 (s), 1249 (s), 1162 (s) cm^{–1}.

HRMS (ESI, [M+Na]⁺) calcd for C₁₆H₂₈O₃SiNa 319.1705, found 319.1701.



(S)-1-((S)-Oxiran-2-yl)hex-5-yn-2-ol (25**)**

Following the procedure of Smith,¹⁵ to a solution of **24** (0.822 g, 2.77 mmol) in toluene (10 mL) at $-85\text{ }^{\circ}\text{C}$ (Et_2O and dry ice bath) was added iodine bromide (5.54 mL, 1M in DCM, 5.54 mmol) dropwise under exclusion of direct light. The reaction mixture was stirred for *ca.* 1 h at that temperature, before it was quenched with 1:1 mixture of 5% aqueous NaHCO_3 and 20% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution. The mixture was warmed to room temperature and partitioned between water and DCM. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the unstable cyclic iodocarbonate **25**, which was used in the following step without purification.

To a solution of crude **25** (~ 2.77 mmol) in MeOH (20 mL) was added K_2CO_3 (1.34 g, 9.70 mmol) and the reaction mixture was stirred for *ca.* 5 h at room temperature (TLC control), before it quenched with saturated aqueous NH_4Cl and partitioned between water and DCM. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /petroleum ether – 1.5:1) afforded the hydroxy epoxide **26** (0.334 g, 2.38 mmol, 86% yield) as a colourless oil.

$R_f = 0.35$ (EtOAc /hexanes – 1:1).

$[\alpha]_D^{20} -30.1$ (c 1.0, CHCl_3).

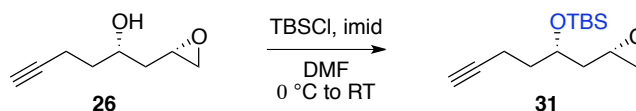
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 4.76 (octet, $J = 4.0$ Hz, 1H), 3.11 (sextet, $J = 3.8$ Hz, 1H), 2.79 (app. t, A of AX_2 , $J_{\text{AX}} = 4.4$ Hz, 1H), 2.51 (dd, M of AMX , $J_{\text{AM}} = 4.9$ Hz,

$J_{MX} = 2.8$ Hz, 1H), 2.37 (d, $J = 3.8$ Hz, 1H), 2.35 (ddd, $J = 10.4, 6.7, 3.1$ Hz, 1H), 1.91 (t, $J = 2.7$ Hz, 1H), 1.89 (app. dt, A of ABX₂, $J_{AB} = 14.4$ Hz, $J_{AX} = 3.9$ Hz, 1H), 1.77-1.69 (m, 2H), 1.52 (app. dt, B of ABX₂, $J_{AB} = 15.4$ Hz, $J_{BX} = 8.0$ Hz, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 84.01 (e), 69.25 (o), 69.00 (e), 50.50 (o), 46.67 (e), 39.73 (e), 35.70 (e), 14.89 (e).

IR (Neat) 3402 (br), 3288 (m), 2922 (m), 2115 (w), 1080 (m) cm⁻¹.

HRMS (CI, [M+NH₄]⁺) calcd for C₈H₁₆O₂N 158.1176, found 158.1171.



***tert*-Butyldimethyl(((*S*)-1-((*S*)-oxiran-2-yl)hex-5-yn-2-yl)oxy)silane (**31**)**

To a solution of **26** (0.461 g, 3.29 mmol) and imidazole (0.672 g, 9.87 mmol) in DMF (10 mL) at 0 °C was added TBSCl (1.239 g, 8.22 mmol). The reaction mixture was warmed to room temperature and stirred for *ca.* 20 h (TLC control), before it was quenched with saturated aqueous NH₄Cl and partitioned between water and Et₂O. Phases were separated and the aqueous layer was washed with Et₂O (2x). The combined organic layers were washed with water, brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et₂O/hexanes – 2%, 4%, 6%) afforded the TBS ester **31** (0.66 g, 2.59 mmol, 79% yield) as a colourless oil.

R_f = 0.7 (EtOAc/hexanes – 1:1).

$[\alpha]_{\text{D}}^{20} -38.1$ (*c* 1.0, CHCl₃).

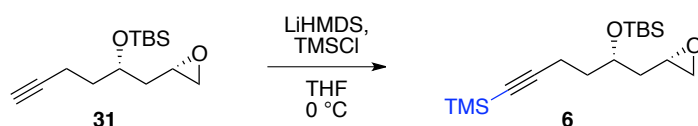
¹H NMR (500 MHz, CDCl₃) δ 4.02 (quintet, $J = 5.7$ Hz, 1H), 3.04 (app. tdd, $J = 6.7, 4.4, 2.6$ Hz, 1H), 2.76 (dd, A of AMX, $J_{AM} = 4.7$ Hz, $J_{AX} = 4.4$ Hz, 1H), 2.45 (dd, M of AMX, $J_{AM} = 5.0$ Hz, $J_{MX} = 2.7$ Hz, 1H), 2.26 (dd, A of ABX, $J_{AB} = 7.2$ Hz,

$J_{AX} = 2.6$ Hz, 1H), 2.25 (dd, B of ABX, $J_{AB} = 7.2$ Hz, $J_{BX} = 2.6$ Hz, 1H), 1.94 (dd, $J = 3.0, 2.3$ Hz, 1H), 1.76 (q, $J = 6.9$ Hz, 2H), 1.75-1.70 (m, 1H), 1.64 (ddd, B of ABXY, $J_{AB} = 14.1$ Hz, $J_{BX} = 6.7$ Hz, $J_{BY} = 4.7$ Hz, 1H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 84.28 (e), 68.84 (o), 68.72 (e), 49.16 (o), 46.83 (e), 40.13 (e), 35.61 (e), 25.92 (o), 18.11 (e), 14.82 (e), -4.41 (o), -4.56 (o).

IR (Neat) 3313 (m), 2929 (m), 1255 (m), 1085 (m) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{14}\text{H}_{26}\text{O}_2\text{NaSi}$ 277.1600, found 277.1590.



***tert*-Butyldimethyl(((*S*)-1-((*S*)-oxiran-2-yl)hex-5-yn-2-yl)oxy)silane (**6**)**

To a cooled to 0 °C solution of **31** (0.959 g, 3.77 mmol) in THF (8 mL) was added LiHMDS (4.52 mL, 1 M in THF, 4.52 mmol). After *ca.* 30 min TMSCl (0.67 mL, 5.28 mmol) was added and the reaction mixture was stirred for *ca.* 1 h at that temperature (TLC control), before it was quenched with saturated aqueous NH_4Cl and partitioned between water and Et_2O . Phases were separated and the aqueous layer was washed with Et_2O (2x). The combined organic layers were washed with water, brine, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /hexanes – 2%, 4%) gave the TMS protected alkyne **6** (1.111 g, 3.40 mmol, 90% yield) as a colourless oil.

$R_f = 0.58$ (Et_2O /hexanes – 1:5).

$[\alpha]_D^{20} -29.8$ (c 1.0, CHCl_3).

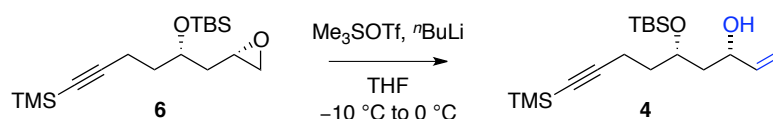
^1H NMR (500 MHz, CDCl_3) δ 4.02 (quintet, $J = 5.7$ Hz, 1H), 3.05 (app. tdd, $J = 6.6, 4.4, 2.5$ Hz, 1H), 2.75 (app. t, A of AX_2 , $J_{AX} = 4.5$ Hz, 1H), 2.45 (dd, M of AMX , J_{AM}

= 5.1 Hz, J_{MX} = 2.7 Hz, 1H), 2.30 (t, J = 7.1 Hz, 2H), 1.80-1.69 (m, 3H), 1.67-1.62 (m, 1H), 0.89 (s, 9H), 0.14 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 107.10 (e), 85.06 (e), 68.95 (o), 49.23 (o), 46.80 (e), 40.11 (e), 35.63 (e), 25.96 (o), 18.15 (e), 16.36 (e), 0.26 (o), -4.42 (o), -4.52 (o).

IR (Neat) 2955 (w), 2929 (w), 2174 (w), 1250 (m), 1083 (m) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{17}\text{H}_{34}\text{O}_2\text{NaSi}$ 349.1995, found 349.1979.



(3*S*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-9-(trimethylsilyl)non-1-en-8-yn-3-ol (4)

To a cooled at $-10\text{ }^{\circ}\text{C}$ solution of Me_3SOTf (1.081 g, 4.78 mmol) in THF (3 mL) slowly added $n\text{BuLi}$ (1.89 mL, 2.5 M in hexanes, 4.73 mmol) and the reaction mixture was stirred for *ca.* 30 min. A solution of **6** (0.156 g, 0.478 mmol) in THF (2.5 mL with washings) was added and the reaction allowed to warm up to $0\text{ }^{\circ}\text{C}$. After *ca.* 3 h at that temperature (TLC control) the reaction was quenched with saturated aqueous NH_4Cl and partitioned between water and DCM. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /petroleum ether – 4%, 6%, 8%) afforded the allylic alcohol **4** (0.150 g, 0.440 mmol, 92% yield) as a colourless oil.

R_f = 0.42 (Et_2O /hexanes – 1:3).

$[\alpha]_{\text{D}}^{20} +10.5$ (c 1.0, CHCl_3).

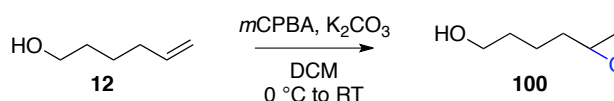
^1H NMR (500 MHz, CDCl_3) δ 5.86 (ddd, J = 16.9, 10.7, 5.9 Hz, 1H), 5.27 (d, J = 17.2 Hz, 1H), 5.09 (d, J = 10.4 Hz, 1H), 4.29-4.26 (m, 1H), 4.06 (app. ddt, J = 11.4, 7.5, 5.5 Hz, 1H), 2.79 (br s, 1H), 2.30 (app. dt, A of ABX_2 , J_{AB} = 17.1 Hz,

$J_{AX} = 6.9$ Hz, 1H), 2.23 (app. dt, B of ABX₂, $J_{AB} = 17.1$ Hz, $J_{BX} = 7.6$ Hz, 1H), 1.78-1.67 (m, 3H), 1.63 (app. dt, B of ABX₂, $J_{AB} = 14.2$ Hz, $J_{BX} = 8.4$ Hz, 1H), 0.90 (s, 9H), 0.14 (s, 9H), 0.12 (s, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 140.90 (o), 114.40 (e), 106.84 (e), 85.13 (e), 71.56 (o), 70.93 (o), 43.02 (e), 36.33 (e), 25.97 (o), 18.06 (e), 15.81 (e), 0.23 (o), -4.01 (o), -4.47 (o).

IR (Neat) 3424 (br), 2956 (w), 2930 (w), 2175 (w), 1644 (w), 1249 (m), 1080 (m) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₁₈H₃₆O₂NaSi₂ 363.2152, found 363.2143.



4-(Oxiran-2-yl)butan-1-ol (**100**)⁴⁸

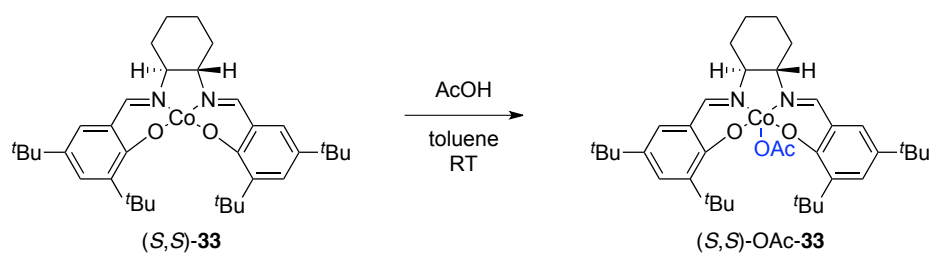
Hex-5-en-1-ol **12** (5.111 g, 51.0 mmol) was dissolved in DCM (100 mL) and treated with 3-chlorobenzoperoxoic acid (12.58 g, 70%, 56.1 mmol), followed by K₂CO₃ (0.564 g, 4.08 mmol) at 0 °C. After *ca.* 15 min the reaction mixture was warmed to room temperature and stirred for *ca.* 12 h (TLC control). The reaction was cooled to 0 °C, quenched with 1 M aq. NaOH and diluted with EtOAc. Phases were separated and the aqueous layer was washed with EtOAc (4x). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et₂O/petroleum ether – 10:1) afforded the epoxy alcohol **100** (4.48 g, 38.5 mmol, 76% yield) as clear oil.

$R_f = 0.14$ (EtOAc/hexanes – 1:1).

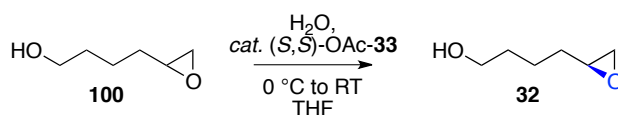
^1H NMR (500 MHz, CDCl_3) δ 3.65 (t, $J = 6.4$ Hz, 2H), 2.94-2.91 (m, 1H), 2.76 (t, A of AX_2 , $J_{\text{AX}} = 4.5$ Hz, 1H), 2.48 (dd, A of AMX , $J_{\text{AM}} = 4.9$ Hz, $J_{\text{MX}} = 2.8$ Hz, 1H), 2.13 (br s, 1H), 1.67-1.48 (m, 6H).

IR (Neat) 3386 (br), 2934 (m), 2861 (m), 1047 (s) cm^{-1} .

Preparation of Jacobsen's catalyst (*S,S*)-OAc-**33**



A solution of (*S,S*)-**33** (0.566 g, 0.937 mmol) in toluene (12 mL) was treated with acetic acid (0.54 mL, 9.37 mmol). The resultant deep brown mixture was stirred for *ca.* 30 min, then concentrated and dried *in vacuo* to afford (*S,S*)-OAc-**33** (0.621 g, 0.937 mmol, 100% yield) as brown solid.



(*S*)-4-(Oxiran-2-yl)butan-1-ol (**32**)

Following the procedure of Jacobsen *et al.*,¹⁶ a (*S,S*)-OAc-**33** catalyst (0.127 g, 0.192 mmol) was suspended in a solution of **100** (4.463 g, 38.4 mmol) in THF (0.5 mL) and treated with water (0.381 mL, 21.13 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for *ca.* 20 h (TLC control). The reaction was directly purified using flash chromatography (silica gel, Et_2O /petroleum ether – 6:1, 8:1, 10:1) to afford the epoxy alcohol **32** (1.30 g, 11.19 mmol, 58% yield, based on 50% conversion) as a brown oil.

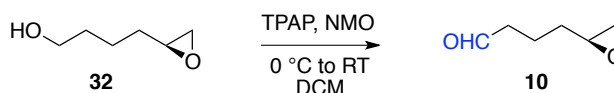
The enantiomeric excess of **32** was determined by chiral HPLC analysis of Bn ether and was shown to be >99% *ee*. Chiral AS-H column, IPA/Hex – 5.0:95.0, 1 mL/min, 25 °C, 210 nm, $t_r(\text{minor}) = 11.7$ min, $t_r(\text{major}) = 10.5$ min.

$R_f = 0.14$ (EtOAc/hexanes – 1:1).

$[\alpha]_D^{20} -6.9$ (c 0.5, CHCl_3).

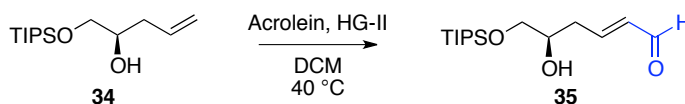
^1H NMR (500 MHz, CDCl_3) δ 3.58 (t, $J = 6.3$ Hz, 2H), 2.91-2.87 (m, 1H), 2.72 (appt, A of AX_2 , $J_{\text{AX}} = 4.5$ Hz, 1H), 2.50 (br s, 1H), 2.45 (dd, A of AMX, $J_{\text{AM}} = 4.9$ Hz, $J_{\text{MX}} = 2.8$ Hz, 1H), 1.61-1.44 (m, 6H).

IR (Neat) 3380 (br), 2934 (m), 2861 (m), 1046 (s) cm^{-1} .



(*S*)-4-(Oxiran-2-yl)butanal (**10**)

To a cooled to 0 °C mixture of **32** (0.507 g, 4.37 mmol) and 4Å molecular sieves (1.5 g) in DCM (15 mL) was added NMO (1.02 g, 8.73 mmol), followed by TPAP (0.077 g, 0.218 mmol). After *ca.* 2 h (TLC control) the reaction mixture was passed through a pad of silica gel (washed with Et_2O /pentane – 5:1). The solution was concentrated at 25 °C (430 Torr) to afford the highly volatile aldehyde (0.389 g, 3.14 mmol, 78% yield) **10**, which was used in the following step without purification.



(*R,E*)-5-((Triethylsilyl)oxy)-6-((triisopropylsilyl)oxy)hex-2-enal (**35**)

A mixture of (*R*)-1-(triisopropylsilyloxy)-pent-4-en-2-ol (**34**)¹⁷ (2.582 g, 9.99 mmol) and acrolein (3.7 mL, 49.9 mmol) was dissolved in DCM (25 mL) and treated with

Chapter 4

Hoveyda-Grubbs 2nd generation catalyst (0.063 g, 0.100 mmol). The reaction mixture was refluxed for *ca.* 2 h (TLC control), then concentrated *in vacuo* and purified by flash chromatography (silica gel, Et₂O/petroleum ether – 1:3, 1:2) to furnish the δ -hydroxy α,β -unsaturated aldehyde **35** (2.684 g, 9.37 mmol, 94% yield) as a brown oil.

R_f = 0.21 (Et₂O/hexanes – 1:1).

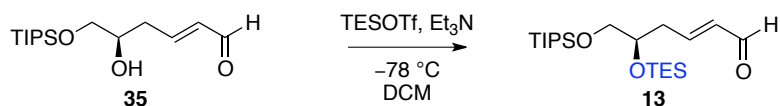
$[\alpha]_{\text{D}}^{20} +9.4$ (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 9.54 (d, *J* = 7.9 Hz, 1H), 6.95 (dt, *J* = 15.6, 7.2 Hz, 1H), 6.20 (ddt, *J* = 15.7, 7.9, 1.4 Hz, 1H), 3.87 (app. qd, *J* = 6.2, 3.8 Hz, 1H), 3.76 (dd, A of ABX, *J*_{AB} = 9.8 Hz, *J*_{AX} = 3.7 Hz, 1H), 3.57 (dd, B of ABX, *J*_{AB} = 9.8 Hz, *J*_{BX} = 6.8 Hz, 1H), 2.61 (br s, 1H), 2.52 (ddd, *J* = 7.2, 6.2, 1.2 Hz, 2H), 1.16-1.09 (m, 3H), 1.07-1.05 (m, 18H).

¹³C NMR (125 MHz, CDCl₃) δ 194.03 (o), 154.54 (o), 134.88 (o), 70.65 (o), 66.97 (e), 36.54 (e), 18.07 (o), 11.98 (o).

IR (Neat) 3436 (br), 2943 (m), 2866 (m), 2724 (w), 1686 (s), 1636 (w), 1117 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₁₅H₃₀O₃NaSi 309.1862, found 309.1847.



To a cooled to $-78\text{ }^\circ\text{C}$ solution of **35** (4.644 g, 16.21 mmol) in DCM (50 mL) was added triethylamine (7.2 mL, 51.9 mmol) and TESOTf (9.16 mL, 40.53 mmol). After *ca.* 10 min (TLC control) the reaction mixture was quenched with saturated aqueous NaHCO₃, warmed to room temperature and partitioned between water and Et₂O. Phases were separated and the aqueous layer was washed with Et₂O (2x). The

combined organic layers were washed with water, brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (Et₂O/hexanes – 2%, 5%) afforded the TES ether **13** (6.44 g, 16.07 mmol, 99% yield) as a colourless oil.

R_f = 0.86 (Et₂O/hexanes – 1:1).

$[\alpha]_D^{20} +7.7$ (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 9.52 (d, *J* = 8.0 Hz, 1H), 6.95 (ddd, *J* = 15.4, 8.0, 7.2 Hz, 1H), 6.18 (ddt, *J* = 15.5, 7.9, 1.2 Hz, 1H), 3.82 (app. ddt, *J* = 8.2, 6.0, 4.7 Hz, 1H), 3.69 (dd, A of ABX, *J*_{AB} = 9.6 Hz, *J*_{AX} = 4.8 Hz, 1H), 3.48 (dd, B of ABX, *J*_{AB} = 9.6 Hz, *J*_{BX} = 8.2 Hz, 1H), 2.69 (dddd, A of ABXYZ, *J*_{AB} = 14.4 Hz, *J*_{AX} = 6.5 Hz, *J*_{AY} = 4.7 Hz, *J*_{AZ} = 1.6 Hz, 1H), 2.53 (dddd, B of ABXYZ, *J*_{AB} = 14.4 Hz, *J*_{BX} = 7.8 Hz, *J*_{BY} = 6.5 Hz, *J*_{BZ} = 1.1 Hz, 1H), 1.12-1.04 (m, 21H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.60 (q, *J* = 7.8 Hz, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 194.18 (o), 155.85 (o), 135.06 (o), 71.89 (o), 67.03 (e), 38.15 (e), 18.10 (o), 11.99 (o), 6.96 (o), 4.97 (e).

IR (Neat) 2944 (m), 2867 (m), 2805 (w), 2729 (w), 1694 (s), 1639 (w), 1119 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₂₁H₄₄O₃NaSi₂ 423.2727, found 423.2707.

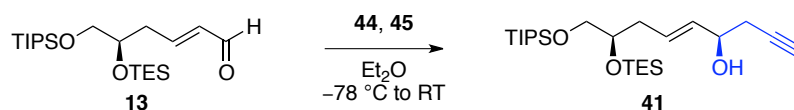


(4*R*,8*R*,*E*)-8-((Triethylsilyl)oxy)-9-((triisopropylsilyl)oxy)non-5-en-1-yn-4-ol (41)

The procedure requires usage of Schlenk techniques and performed under an atmosphere of argon at all operational steps!

Following a procedure of Corey *et al.*,²¹ to a suspension of (*R,R*)-**42** (3.09 g, 5.94 mmol) in DCM (32 mL) at 0 °C was added BBr₃ (5.49 mL, 1 M in DCM,

5.49 mmol) dropwise. The reaction mixture stirred for *ca.* 15 and then brought to room temperature. After *ca.* 40 min the RM was concentrated under reduced pressure using a dry ice trap. The resultant yellow solid was dissolved in DCM (32 mL), cooled to 0 °C and treated with a solution of propargyl stannane **46** (1.984 g, 5.10 mmol) in DCM (6 mL). The reaction mixture was stirred for *ca.* 3.5 h at 0 °C and *ca.* 30 min at room temperature, before it was cooled to –78 °C and treated with a cooled to –78 °C solution of **13** (0.808 g, 3 mmol) in DCM (6 mL) using a double-ended cannula. The reaction mixture was left to slowly warm up to room temperature and stirred for *ca.* 16 h (TLC control), before it was quenched with pH 7 buffer and diluted with DCM. Phases were separated and the aqueous layer was washed with DCM (2x). Combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to furnish crude solid product, which was treated with 25% EtOAc/hexanes solution, cooled to 0 °C and filtered to recover the precipitated ligand. The mother liquor was concentrated *in vacuo* and purified by flush chromatography (DCM/Hex – 10:1, Et₂O/DCM – 1:25 to recover ligand) to afford the homopropargylic alcohol **41** (0.698 g, 2.255 mmol, 75% yield) as slightly yellow oil.



The procedure requires usage of Schlenk techniques and performed under an atmosphere of argon at all operational steps!

Following the procedure of Soderquist *et al.*,²² to a suspension of 1(*R*)-**44** (0.243 g, 0.655 mmol) in Et₂O (3.1 mL) was added freshly prepared allenylmagnesium bromide (**45**) (0.80 mL, 0.653 mmol). The reaction warmed to room temperature

and stirred for *ca.* 1 h, before the solvent was removed using a dry ice trap. The residue was triturated with hexanes (5 mL) and solution carefully transferred from precipitates to another flask using syringe (5x) and concentrated *in vacuo*. The residue was dissolved in Et₂O (3.1 mL), cooled to -78 °C and treated with **37** (0.218 g, 0.544 mmol) in Et₂O (2 mL with washings). After *ca.* 3 h (TLC control), the reaction mixture warmed to room temperature and concentrated *in vacuo*. Pseudoephedrine (0.108 g, 0.655 mmol) in MeCN (3.1 mL) was added and the solution was refluxed for *ca.* 4 h, before it was concentrated and purified by flash chromatography (Et₂O/hexanes – 1:6) to furnish the homopropargylic alcohol **41** (0.155 g, 0.352 mmol, 65% yield) as a colourless oil.

R_f = 0.19 (Et₂O/Hexanes – 1:5).

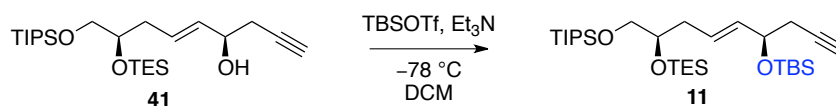
$[\alpha]_{\text{D}}^{20} +13.5$ (*c* 0.5, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 5.80 (dt, *J* = 15.1, 7.4 Hz, 1H), 5.61 (dd, *J* = 15.5, 6.6 Hz, 1H), 4.25 (q, *J* = 6.0 Hz, 1H), 3.72 (app. dtd, *J* = 11.4, 6.1, 1.2 Hz, 1H), 3.61 (dd, A of ABX, *J*_{AB} = 9.6 Hz, *J*_{AX} = 5.0 Hz, 1H), 3.49 (dd, B of ABX, *J*_{AB} = 9.6 Hz, *J*_{BX} = 7.2 Hz, 1H), 2.43 (ddd, A of AMXY, *J*_{AM} = 16.6 Hz, *J*_{AX} = 5.3 Hz, *J*_{AY} = 2.6 Hz, 1H), 2.43-2.37 (m, 3H), 2.20 (app. dt, B of ABX₂, *J*_{AB} = 13.8 Hz, *J*_{BX} = 2.6 Hz, 1H), 2.04 (t, *J* = 2.6 Hz, 1H), 1.96 (br s, 1H), 1.10-1.03 (m, 21H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.59 (q, *J* = 8.0 Hz, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 133.04 (o), 129.47 (o), 80.61 (e), 72.73 (o), 70.77 (o), 70.67 (e), 66.98 (e), 37.29 (e), 27.56 (e), 18.00 (o), 11.93 (o), 6.88 (o), 4.94 (e).

IR (Neat) 3410 (w), 3314 (w), 2943 (m), 2867 (m), 1462 (m), 1109 (m) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₂₄H₄₈O₃NaSi₂ 463.3040, found 463.3052.



(5*R*,9*R*,*E*)-12,12-Diisopropyl-2,2,3,3,13-pentamethyl-5-(prop-2-yn-1-yl)-9-((triethylsilyl)oxy)-4,11-dioxo-3,12-disilatetradec-6-ene (11)

To a cooled to -78°C solution of **41** (0.619 g, 1.403 mmol) and 2,6-lutidine (0.26 mL, 2.245 mmol) in DCM (5 mL) was added TBSOTf (0.42 mL, 1.824 mmol). After *ca.* 5 min (TLC control) the reaction mixture was quenched with saturated aqueous NaHCO_3 , warmed to room temperature and partitioned between water and Et_2O . Phases were separated and the aqueous layer was washed with Et_2O (2x). The combined organic layers were washed with water, brine, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /hexanes – 1:80) gave the TBS ether **11** (0.70 g, 1.26 mmol, 90% yield) as a colourless oil.

$R_f = 0.81$ (Et_2O /Hexanes – 1:5).

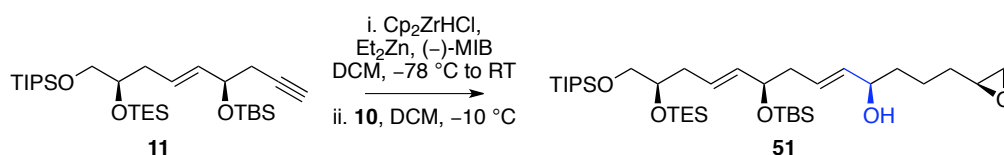
$[\alpha]_D^{20} +4.3$ (*c* 0.5, CHCl_3).

^1H NMR (500 MHz, CDCl_3) δ 5.70 (dt, $J = 14.9, 7.3$ Hz, 1H), 5.56 (dd, $J = 15.4, 6.1$ Hz, 1H), 4.23 (q, $J = 6.2$ Hz, 1H), 3.73 (quintet, $J = 5.6$ Hz, 1H), 3.60 (dd, A of ABX, $J_{AB} = 9.7$ Hz, $J_{AX} = 5.3$ Hz, 1H), 3.52 (dd, B of ABX, $J_{AB} = 9.7$ Hz, $J_{BX} = 6.6$ Hz, 1H), 2.38 (ddd, A of ABXY, $J_{AB} = 16.5$ Hz, $J_{AX} = 6.3$ Hz, $J_{AY} = 2.6$ Hz, 1H), 2.37-2.34 (m, 1H), 2.31 (ddd, B of ABXY, $J_{AB} = 16.5$ Hz, $J_{BX} = 6.6$ Hz, $J_{BY} = 2.6$ Hz, 1H), 2.20 (app. dt, B of ABX₂, $J_{AB} = 13.6$ Hz, $J_{BX} = 6.7$ Hz, 1H), 1.95 (t, $J = 2.5$ Hz, 1H), 1.10-1.03 (m, 21H), 0.95 (t, $J = 8.0$ Hz, 9H), 0.89 (s, 9H), 0.60 (q, $J = 7.9$ Hz, 6H), 0.08 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 133.26 (o), 127.43 (o), 81.83 (e), 72.99 (o), 72.15 (o), 69.85 (e), 67.04 (e), 37.22 (e), 28.75 (e), 26.00 (o), 18.37 (e), 18.16 (o), 12.10 (o), 7.04 (o), 5.12 (e), -4.29 (o), -4.63 (o).

IR (Neat) 3316 (w), 2951 (m), 2867 (m), 1462 (w), 1100 (s) cm^{-1} .

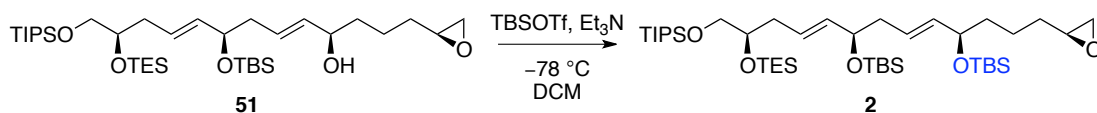
HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{30}\text{H}_{62}\text{O}_3\text{NaSi}_3$ 577.3905, found 577.3903.



(4*R*,5*E*,8*R*,9*E*,12*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-1-((*S*)-oxiran-2-yl)-12-((triethylsilyl)oxy)-13-((triisopropylsilyl)oxy)trideca-5,9-dien-4-ol (51)

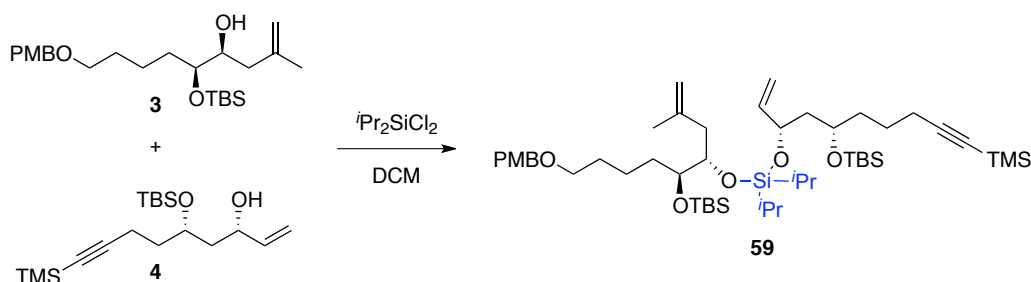
To a suspension of Schwartz reagent (0.057 g, 0.220 mmol) in DCM (1.6 mL) at 0 °C was added neat **11** (0.111 g, 0.2 mmol) using a microliter syringe. The reaction mixture was warmed to room temperature and stirred for *ca.* 30 min until precipitates dissolved. The resultant slightly yellow solution was cooled to -78 °C and Me_2Zn (0.183 mL, 1.2 M in toluene, 0.220 mmol) was added, followed by $(-)$ -MIB (4.8 mg, 0.020 mmol) as a solution in DCM (0.5 mL with washings). After *ca.* 30 min the reaction mixture was warmed to room temperature and stirred for *ca.* 10 min., then cooled to -10 °C and treated with a solution of **10** (0.0457 g, 0.4 mmol) in a 10:1 mixture of hexanes/DCM (0.2 mL with washings). After 13 h (TLC control) the reaction was quenched with saturated aqueous NH_4Cl and partitioned between DCM and water. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /hexanes – 1:3, 1:2, 1:1) afforded the allylic alcohol **51** (0.058 g, 0.086 mmol, 43% yield) as clear oil.

For characterization, see p. 272.



To a cooled to $-78\text{ }^{\circ}\text{C}$ solution of **51** and 2,6-lutidine (6.6 μL , 0.057 mmol) in DCM (1.3 mL) was added TBSOTf (6.6 μL , 0.029 mmol). After *ca.* 15 min (TLC control) the reaction mixture was quenched with saturated aqueous NaHCO_3 , warmed to room temperature and partitioned between water and Et_2O . Phases were separated and the aqueous layer was washed with Et_2O (2x). The combined organic layers were washed with water, brine, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , Et_2O /hexanes – 1:30) afforded the TBS ether **2** (0.0105 g, 0.013 mmol, 93% yield) as a colourless oil.

For characterization, see p. 273.



(5*S*,6*S*,10*S*,12*S*)-8,8-Diisopropyl-5-(4-((4-methoxybenzyl)oxy)butyl)-

2,2,3,3,14,14,15,15-octamethyl-6-(2-methylallyl)-12-(5-(trimethylsilyl)pent-4-yn-

1-yl)-10-vinyl-4,7,9,13-tetraoxa-3,8,14-trisilahexadecane (59**)**

The procedure requires usage of Schlenk techniques and performed under an atmosphere of argon at all operational steps! The 50 mL round bottom Schlenk flask was charged with dry imidazole (0.340 g, 5.00 mmol) and DCM (15 mL). The solution was cooled to $0\text{ }^{\circ}\text{C}$ and $i\text{Pr}_2\text{SiCl}_2$ (0.81 mL, 4.50 mmol) was added dropwise. After *ca.* 10 min a solution of **3** (0.423 g, 1 mmol) in DCM (3 mL) was

added using a syringe pump over *ca.* 3 h and the reaction left to warm to room temperature. After *ca.* 16 h the reaction mixture was concentrated under reduced pressure using a dry ice trap. The residue was triturated with hexane (10 mL) and the solution was carefully decanted from precipitates using a syringe into a separate 100 mL Kugelrohr flask (3x). The hexane washings were concentrated under reduced pressure using a dry ice trap and the residue was heated at 75 °C *in vacuo* (1 Torr) for *ca.* 3 h to remove the excess of $t\text{-Pr}_2\text{SiCl}_2$. The crude monochloroalkoxysilane was cooled to 0 °C and imidazole (0.340 g, 5.00 mmol) in DCM (2 mL with washings) was added, followed by **4** (0.286 g, 0.840 mmol) in DCM (3 mL with washings) and the reaction was warmed to room temperature. After *ca.* 15 h (TLC control) the reaction mixture was quenched with saturated aqueous NH_4Cl and partitioned between Et_2O and water. Phases were separated and the aqueous layer was washed with Et_2O (2x). The combined organic layers were washed with water (2x), brine, dried (MgSO_4), filtered and concentrated. Purification by flash chromatography (silica gel, Et_2O /hexanes – 1:22, 1:20) afforded the mixed silaketal **59** (0.615 g, 0.702 mmol, 84% yield) as a colourless oil.

$R_f = 0.74$ (EtOAc /hexanes – 1:2).

$[\alpha]_D^{20} -8.2$ (c 1.0, CHCl_3).

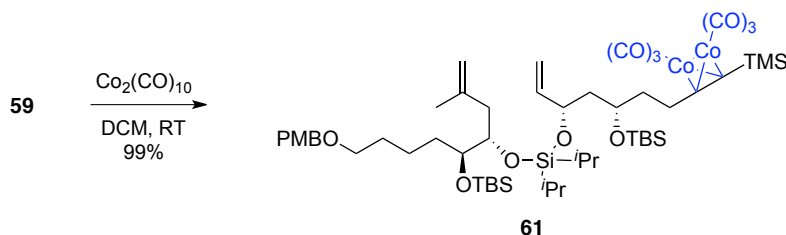
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.27-7.25 (m, 2H), 6.87-6.86 (m, 2H), 5.82 (ddd, $J = 17.2, 10.4, 6.8$ Hz, 1H), 5.19 (d, $J = 17.2$ Hz, 1H), 5.08 (d, $J = 10.4$ Hz, 1H), 4.76 (s, 2H), 4.45-4.40 (m, 3H), 3.97 (ddd, $J = 9.2, 3.8, 2.4$ Hz, 1H), 3.86-3.82 (m, 1H), 3.79 (s, 3H), 3.44 (t, $J = 6.5$ Hz, 2H), 2.37 (d, A of AB, $J_{AB} = 13.3$ Hz, 1H), 2.28 (ddd, A of ABXY, $J_{AB} = 17.0$ Hz, $J_{AX} = 7.9$ Hz, $J_{AY} = 6.6$ Hz, 1H), 2.27-2.18 (m, 1H), 2.02 (dd, B of ABX, $J_{AB} = 13.6$ Hz, $J_{BX} = 9.4$ Hz, 1H), 1.80 (ddd, A of ABXY, $J_{AB} = 13.3$ Hz, $J_{AX} = 7.8$ Hz, $J_{AY} = 5.3$ Hz, 1H), 1.77-1.50 (m, 8H), 1.75 (s, 3H), 1.32-1.21 (m,

2H), 1.06-1.00 (m, 12H), 0.95-0.91 (m, 2H), 0.89 (s, 9H), 0.88 (s, 9H), 0.14 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 159.18 (e), 143.55 (e), 141.13 (o), 130.97 (e), 129.28 (o), 114.87 (e), 113.84 (o), 112.96 (e), 107.19 (e), 84.70 (e), 75.05 (o), 73.52 (o), 72.62 (e), 71.22 (o), 70.32 (e), 68.12 (o), 55.35 (o), 45.41 (e), 39.27 (e), 36.59 (e), 30.23 (e), 29.95 (e), 26.02 (o), 23.54 (e), 23.12 (o), 18.13 (e), 17.79 (o), 17.76 (o), 17.70 (o), 17.69 (o), 15.82 (e), 13.29 (o), 13.08 (o), 0.26 (o), -3.76 (o), -4.03 (o), -4.15 (o), -4.33 (o).

IR (Neat) 2929 (m), 2958 (m), 2174 (w), 1646 (w), 1614 (w), 1513 (w), 1098 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{48}\text{H}_{90}\text{O}_6\text{NaSi}_4$ 897.5712, found 897.5717.



Dicobalt hexacarbonyl complex of (5*S*,6*S*,10*S*,12*S*)-8,8-diisopropyl-5-(4-((4-methoxybenzyl)oxy)butyl)-2,2,3,3,14,14,15,15-octamethyl-6-(2-methylallyl)-12-(5-(trimethylsilyl)pent-4-yn-1-yl)-10-vinyl-4,7,9,13-tetraoxa-3,8,14-trisilahehexadecane (61)

To a solution of **59** (1.186 g, 1.354 mmol) in DCM (15 mL) was added a solid cobalt carbonyl complex (0.648 g, 1.896 mmol). After 1 h (TLC control) the reaction mixture was concentrated and purified by flash chromatography (silica gel, Et_2O /hexanes – 1:20) to afford the dicobalt adduct **61** (1.56 g, 1.336 mmol, 99% yield) as brown oil.

R_f = 0.40 (Et_2O /hexanes – 1:10).

Chapter 4

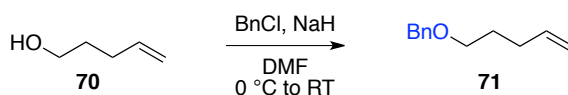
$[\alpha]_{\text{D}}^{20} -2.2$ (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.28-7.25 (m, 2H), 6.89-6.86 (m, 2H), 5.83 (ddd, $J = 17.5, 10.3, 7.1$ Hz, 1H), 5.20 (d, $J = 17.2$ Hz, 1H), 5.12 (dd, $J = 10.4, 0.7$ Hz, 1H), 4.76 (s, 2H), 4.45 (d, A of AB, $J_{AB} = 11.6$ Hz, 1H), 4.43 (d, B of AB, $J_{AB} = 11.6$ Hz, 1H), 4.43-4.39 (m, 1H), 3.99 (ddd, $J = 9.4, 4.1, 2.3$ Hz, 1H), 3.84 (sextet, $J = 4.6$ Hz, 1H), 3.80 (s, 3H), 3.74 (ddd, $J = 9.3, 4.0, 2.1$ Hz, 1H), 3.45 (app. td, $J = 6.6, 1.1$ Hz, 2H), 2.97 (app. dt, A of ABX₂, $J_{AB} = 13.3$ Hz, $J_{AX} = 5.4$ Hz, 1H), 2.92 (app. dt, B of ABX₂, $J_{AB} = 15.2$ Hz, $J_{BX} = 5.4$ Hz, 1H), 2.37 (d, A of AB, $J_{AB} = 12.5$ Hz, 1H), 2.02 (dd, B of ABX, $J_{AB} = 13.6$ Hz, $J_{BX} = 9.5$ Hz, 1H), 1.96 (ddd, A of ABXY, $J_{AB} = 13.4$ Hz, $J_{AX} = 8.6$ Hz, $J_{AY} = 4.8$ Hz, 1H), 1.88 (app. dt, B of ABX₂, $J_{AB} = 11.6$ Hz, $J_{BX} = 5.8$ Hz, 1H), 1.79-1.72 (m, 1H), 1.75 (s, 3H), 1.70-1.51 (m, 5H), 1.32-1.19 (m, 2H), 1.04 (d, $J = 7.1$ Hz, 3H), 1.03 (d, $J = 7.1$ Hz, 3H), 1.02 (d, $J = 7.2$ Hz, 3H), 1.01 (d, $J = 7.2$ Hz, 3H), 0.98-0.92 (m, 2H), 0.90 (s, 9H), 0.89 (s, 9H), 0.30 (s, 9H), 0.08 (s, 3H), 0.07 (s, 6H), 0.05 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 200.61 (e), 159.21 (e), 143.66 (e), 141.19 (o), 131.01 (e), 129.30 (o), 115.32 (e), 113.86 (o), 112.88 (e), 112.74 (e), 79.21 (e), 75.07 (o), 73.58 (o), 72.63 (e), 71.59 (o), 70.36 (e), 68.58 (o), 55.39 (o), 45.90 (e), 40.68 (e), 39.19 (e), 30.22 (e), 30.17 (e), 29.89 (e), 25.99 (o), 25.96 (o), 23.55 (e), 23.10 (o), 18.13 (e), 17.79 (o), 17.69 (o), 17.62 (o), 17.58 (o), 13.26 (o), 13.11 (o), 0.81 (o), -3.75 (o), -4.05 (o), -4.11(o), -4.38 (o).

IR (Neat) 2950 (w), 2926 (w), 2859 (w), 2076 (m), 2010 (m), 2044 (m), 1614 (w), 1687 (w), 1097 (m) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₅₄H₉₀O₁₂NaSi₄⁵⁴Co₂ 1183.4059, found 1183.4071.



((Pent-4-en-1-yloxy)methyl)benzene (71)⁴⁹

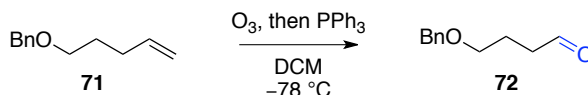
To a cooled to 0 °C suspension of sodium hydride (3.12 g, 60% in mineral oil, 78 mmol) in DMF (120 mL) was added 4-penten-1-ol (**70**) (5.17 g, 60 mmol), followed by benzylbromide (9.33 mL, 78 mmol). The solution warmed to room temperature and stirred for *ca.* 16 h (TLC control). The reaction was cooled to 0 °C and quenched with saturated aqueous NH₄Cl. The solution was partitioned between Et₂O and water. Layers were separated and the aqueous phase was washed with Et₂O (2x). The combined organic phases were washed with water, brine, dried with MgSO₄, filtered and concentrated *in vacuo* to afford the crude alcohol **71**, which was used in the following step without purification.

An analytical sample was obtained by purification using flash chromatography (silica gel, Et₂O/petroleum ether – 1:50) as a colourless oil.

R_f = 0.73 (Et₂O/hexanes – 1:1).

¹H NMR (500 MHz, CDCl₃) δ 7.42-7.37 (m, 4H), 7.35-7.30 (m, 1H), 5.88 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.08 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.02 (dd, *J* = 10.2, 1.4 Hz, 1H), 4.55 (s, 2H), 3.54 (t, *J* = 6.5 Hz, 2H), 2.20 (q, *J* = 7.2 Hz, 2H), 1.77 (app. dt, *J* = 14.3, 7.0 Hz, 2H).

IR (Neat) 3066(w), 2936 (w), 2853 (w), 1640 (w), 1101 (s) cm⁻¹.



4-(Benzyloxy)butanal (72)⁵⁰

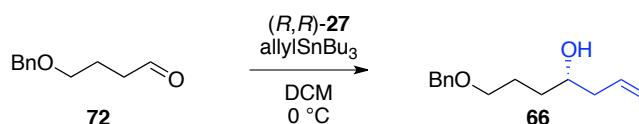
Crude alkene **71** (10.58 g, 60 mmol) was dissolved in DCM (300 mL) and cooled to –78 °C. O₃ was bubbled through the reaction mixture for *ca.* 45 min, until it became

slightly blue (TLC control). Then the solution was flushed with air, argon and treated with solid PPh_3 (31.5 g, 120 mmol). The reaction was warmed to room temperature and stirred for *ca.* 16 h, before it was dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /petroleum ether – 1:7, 1:3) furnished aldehyde **72** (9.51 g, 53.4 mmol, 89% yield over 2 steps) as a colourless oil.

$R_f = 0.4$ (Et_2O /hexanes – 1:3).

^1H NMR (500 MHz, CDCl_3) δ 9.79 (s, 1H), 7.36-7.26 (m, 5H), 4.49 (s, 2H), 3.51 (t, $J = 6.1$ Hz, 2H), 2.56 (app. td, $J = 7.1, 1.2$ Hz, 2H), 1.96 (quintet, $J = 6.6$ Hz, 2H).

IR (Neat) 3031 (w), 2931 (w), 2858 (m), 2724 (w), 1721 (s), 1093 (s) cm^{-1} .



(S)-7-(Benzyloxy)hept-1-en-4-ol (66)³¹

To a cooled to -15°C stock solution of (*R,R*)-**27** (53 mL, 0.1 M in DCM, 5.3 mmol) was added **14** (9.51 g, 53.4 mmol) in DCM (10 mL with washings) and allyltributylstannane (24.2 mL, 78 mmol). The reaction mixture was warmed to 0°C and stirred for *ca.* 24 h (TLC control), before it was quenched with saturated aqueous NaHCO_3 and partitioned between water and Et_2O . Phases were separated and the aqueous layer was washed with Et_2O (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /petroleum ether – 1:4, 1:3, 1:3) afforded the homoallylic alcohol **66** (9.41 g, 42.7 mmol, 85% yield) as a colourless oil. Enantiomeric excess of **66** was determined by chiral HPLC analysis and was shown to be 92-95% *ee*. Chiral AS-H

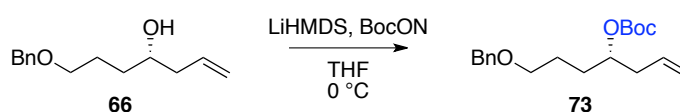
column, IPA/Hex – 3.0:97.0, 0.5 mL/min, 25 °C, 210 nm, t_r (minor) = 23.5 min, t_r (major) = 38.3 min.

$[\alpha]_D^{20}$ –6.4 (c 1.0, CHCl_3), Lit. $[\alpha]_D^{20}$ –8.8 (c 1.16, MeOH).³¹

R_f = 0.12 (Et_2O /hexanes – 1:3).

^1H NMR (500 MHz, CDCl_3) δ 7.38-7.33 (m, 4H), 7.32-7.26 (m, 1H), 5.84 (ddt, J = 17.0, 10.2, 7.0 Hz, 1H), 5.14-5.10 (m, 2H), 4.52 (s, 2H), 3.66 (septet, J = 4.1 Hz, 1H), 3.51 (t, J = 6.1 Hz, 2H), 2.56 (br s, 1H), 2.28 (ddd, A of ABXY, J_{AB} = 13.6 Hz, J_{AX} = 6.7 Hz, J_{AY} = 5.5 Hz, 1H), 2.19 (app. dt, B of ABX₂, J_{AB} = 14.3 Hz, J_{BX} = 7.2 Hz, 1H), 1.81-1.69 (m, 2H), 1.68-1.61 (m, 1H), 1.50 (ddd, B of ABXY, J_{AB} = 14.4 Hz, J_{BX} = 8.0 Hz, J_{BY} = 5.8 Hz, 1H).

IR (Neat) 3423 (br), 2955 (m), 2922 (m), 1640 (w), 1622 (w), 1073 (s) cm^{-1} .



(S)-7-(Benzyloxy)hept-1-en-4-yl *tert*-butyl carbonate (73)

To a cooled to 0 °C solution of **66** (9.41 g, 42.7 mmol) in THF (140 mL) was added LiHMDS (107 mL, 1 M in THF, 107 mmol) dropwise. The reaction mixture stirred for *ca.* 10 min and treated with a solution of BocON (26.35 g, 107 mmol) in THF (50 mL with washings). After *ca.* 15 min (TLC control) the reaction mixture was quenched with saturated aqueous NH_4Cl and partitioned between water and Et_2O . Phases were separated and the aqueous layer was washed with Et_2O (3x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /petroleum ether – 1:20, 1:11, 1:10) afforded carbonate **73** (13.0 g, 40.6 mmol, 95% yield) as a colourless oil.

R_f = 0.42 (Et_2O /hexanes – 1:3).

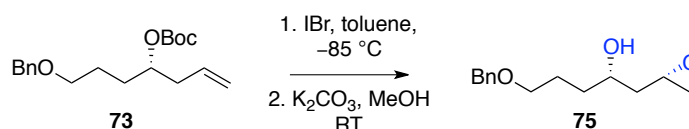
$[\alpha]_{\text{D}}^{20} -15.6$ (c 1.0, CHCl_3).

^1H NMR (500 MHz, CDCl_3) δ 7.36-7.32 (m, 4H), 7.29-7.26 (m, 1H), 5.78 (ddt, $J = 17.1, 10.1, 7.1$ Hz, 1H), 5.11 (dd, $J = 17.3, 1.7$ Hz, 1H), 5.08 (dd, $J = 11.6, 1.2$ Hz, 1H), 4.72 (app. tt, $J = 7.3, 5.5$ Hz, 1H), 4.50 (s, 2H), 3.50-3.44 (m, 2H), 2.36 (t, $J = 6.7$ Hz, 2H), 1.74-1.62 (m, 4H), 1.48 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ 153.40 (e), 138.52 (e), 133.51 (o), 128.38 (o), 127.62 (o), 127.55 (o), 117.90 (e), 81.71 (e), 76.28 (o), 72.87 (e), 69.89 (e), 38.84 (e), 30.39 (e), 27.83 (o), 25.66 (e).

IR (Neat) 2980 (w), 2856 (w), 1732 (s), 1643 (w), 1093 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{19}\text{H}_{28}\text{O}_4\text{Na}$ 343.1885, found 343.1886.



(S)-5-(Benzyloxy)-1-((S)-oxiran-2-yl)pentan-2-ol (75)

Following the procedure of Smith *et al.*,¹⁵ to a solution of **73** (2.985 g, 9.32 mmol) in toluene (28 mL) at -85 °C (Et_2O and dry ice bath) was added iodine bromide (5.54 mL, 1 M in DCM, 5.54 mmol) under exclusion of direct light. The reaction mixture was stirred for *ca.* 15 min at that temperature (TLC control), before it was quenched with 1:1 mixture of 5% aqueous NaHCO_3 and 20% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution. The mixture was warmed to room temperature and partitioned between water and DCM. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the unstable cyclic iodocarbonate **74**, which was used in the following step without purification.

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To a solution of crude **74** (~9.32 mmol) in MeOH (28 mL) was added K₂CO₃ (3.86 g, 28.0 mmol) and the reaction mixture was stirred for *ca.* 4.5 h at room temperature (TLC control), before it quenched with saturated aqueous NH₄Cl and partitioned between water and DCM. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et₂O/hexanes – 1:5) afforded the hydroxy epoxide **75** (1.779 g, 7.53 mmol, 81% yield) as a colourless oil.

R_f = 0.2 (EtOAc/hexanes – 1:1).

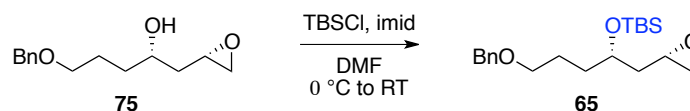
$[\alpha]_{\text{D}}^{20}$ –9.5 (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.36-7.32 (m, 3H), 7.30-7.26 (m, 2H), 4.51 (s, 2H), 3.90-3.82 (m, 1H), 3.53 (app. dt, A of ABX₂, *J*_{AB} = 9.5 Hz, *J*_{AX} = 5.9 Hz, 1H), 3.51 (app. dt, B of ABX₂, *J*_{AB} = 9.9 Hz, *J*_{BX} = 6.0 Hz, 1H), 3.08 (app. dtd, *J* = 7.0, 4.2, 2.8 Hz, 1H), 3.00 (br s, 1H), 2.77 (app. t, A of AX₂, *J*_{AX} = 4.5 Hz, 1H), 2.49 (dd, M of AMX, *J*_{AM} = 5.0 Hz, *J*_{MX} = 2.8 Hz, 1H), 1.79-1.72 (m, 3H), 1.71-1.64 (m, 1H), 1.62-1.52 (m, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 138.10 (e), 128.46 (o), 127.76 (o), 127.72 (o), 73.09 (e), 70.43 (e), 69.93 (o), 50.47 (o), 46.72 (e), 39.83 (e), 34.79 (e), 26.16 (e).

IR (Neat) 3426 (br), 2921 (w), 2856 (w), 1093 (s) cm^{–1}.

HRMS (CI, [M+H]⁺) calcd for C₁₄H₂₁O₃ 237.1485, found 237.1488.



(((*S*)-5-(Benzyloxy)-1-((*S*)-oxiran-2-yl)pentan-2-yl)oxy)(*tert*-butyl)dimethylsilane (65)

To a solution of **75** (1.779 g, 7.53 mmol) in DMF (26 mL) at room temperature was added TMEDA (2.80 mL, 18.82 mmol) followed by TBSCl (2.269 g, 15.06 mmol). The reaction mixture was stirred for *ca.* 16 h (TLC control), before it was quenched with saturated aqueous NH₄Cl and partitioned between water and Et₂O. Phases were separated and the aqueous layer was washed with Et₂O (2x). The combined organic layers were washed with water, brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et₂O/petroleum ether – 1:13, 1:10) afforded TBS ether **65** (2.555 g, 7.29 mmol, 97% yield) as a colourless oil.

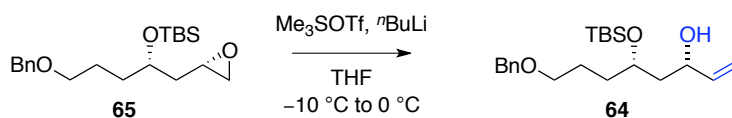
$[\alpha]_{\text{D}}^{20} -14.5$ (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.37-7.32 (m, 4H), 7.31-7.26 (m, 1H), 4.51 (s, 2H), 3.91 (quintet, *J* = 5.5 Hz, 1H), 3.49 (t, *J* = 6.0 Hz, 2H), 3.04 (app. ddt, *J* = 6.8, 4.1, 2.7 Hz, 1H), 2.75 (app. t, A of AX₂, *J*_{AX} = 4.5 Hz, 1H), 2.45 (dd, M of AMX, *J*_{AM} = 5.1 Hz, *J*_{MX} = 2.7 Hz, 1H), 1.76-1.59 (m, 6H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 138.63 (e), 128.37 (o), 127.64 (o), 127.52 (o), 72.87 (e), 70.42 (e), 70.17 (o), 49.42 (o), 46.81 (e), 40.19 (e), 33.72 (e), 25.88 (o), 25.80 (e), 18.06 (e), -4.49 (o), -4.52 (o).

IR (Neat) 2923 (w), 2857 (w), 1095 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₂₀H₃₄O₃NaSi 373.2175, found 373.2162.



(3*S*,5*S*)-8-(Benzyloxy)-5-((*tert*-butyldimethylsilyl)oxy)oct-1-en-3-ol (64)

To a cooled at $-10\text{ }^{\circ}\text{C}$ solution of Me_3SOTf (8.24 g, 36.4 mmol) in THF (30 mL) slowly added $^n\text{BuLi}$ (14.3 mL, 2.5 M in hexanes, 35.7 mmol) and the reaction mixture was stirred for *ca.* 30 min. A solution of **65** (2.555 g, 7.29 mmol) in THF (5 mL with washings) was added and the reaction allowed to warm up to $0\text{ }^{\circ}\text{C}$. After *ca.* 16 h at that temperature (TLC control) the reaction was quenched with saturated aqueous NH_4Cl and partitioned between water and DCM. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /petroleum ether – 1:5, 1:4, 1:3) afforded the allylic alcohol **64** (2.45 g, 6.72 mmol, 92% yield) as a colourless oil.

$R_f = 0.21$ (Et_2O /hexanes – 1:3).

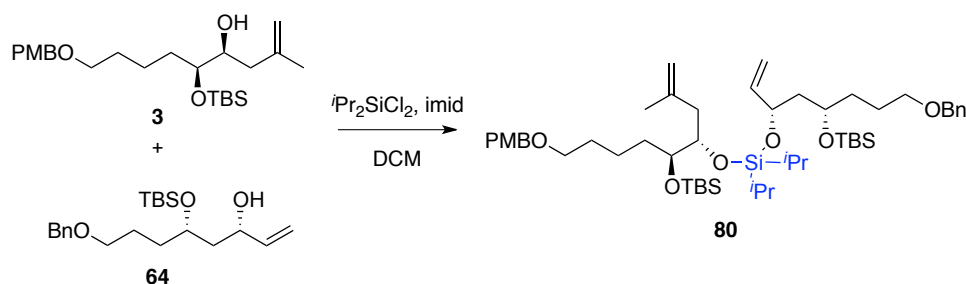
$[\alpha]_D^{20} +20.8$ (*c* 1.0, CHCl_3).

^1H NMR (500 MHz, CDCl_3) δ 7.36-7.31 (m, 4H), 7.30-7.26 (m, 1H), 5.85 (ddd, $J = 16.9, 10.7, 6.0$ Hz, 1H), 5.26 (dt, $J = 17.2, 1.3$ Hz, 1H), 5.09 (dt, $J = 10.5, 1.2$ Hz, 1H), 4.50 (s, 2H), 4.27 (q, $J = 6.0$ Hz, 1H), 3.98 (quintet, $J = 5.8$ Hz, 1H), 3.47 (app. dt, A of ABX_2 , $J_{AB} = 9.1$ Hz, $J_{AX} = 5.8$ Hz, 1H), 3.46 (app. dt, B of ABX_2 , $J_{AB} = 9.2$ Hz, $J_{BX} = 6.0$ Hz, 1H), 3.15 (br s, 1H), 1.69-1.58 (m, 4H), 1.66 (t, $J = 5.4$ Hz, 2H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 140.82 (o), 138.52 (e), 128.39 (o), 127.62 (o), 127.57 (o), 114.17 (e), 72.86 (e), 72.32 (o), 71.87 (o), 70.36 (e), 43.00 (e), 34.40 (e), 25.88 (o), 24.91 (e), 17.97 (e), -3.97 (o), -4.64 (o).

IR (Neat) 3432 (br), 2947 (m), 2856 (m), 1644 (w), 1060 (m) cm^{-1} .

HRMS (ESI, $[M+Na]^+$) calcd for $C_{21}H_{36}O_3NaSi$ 387.2331, found 387.2323.



(5*S*,6*S*,10*S*,12*S*)-12-(3-(Benzyloxy)propyl)-8,8-diisopropyl-5-((4-methoxybenzyl)oxy)butyl)-2,2,3,3,14,14,15,15-octamethyl-6-(2-methylallyl)-10-vinyl-4,7,9,13-tetraoxa-3,8,14-trisilahexadecane (80)

The procedure requires usage of Schlenk techniques and performed under an atmosphere of argon at all operational steps! The 50 mL round bottom Schlenk flask was charged with imidazole (0.340 g, 5.00 mmol) and dissolved in DCM (15 mL). The solution was cooled to 0 °C and iPr_2SiCl_2 (0.81 mL, 4.50 mmol) was added dropwise. After *ca.* 10 min a solution of **3** (0.423 g, 1 mmol) in DCM (3 mL) was added using a syringe pump over *ca.* 3 h and the reaction left to warm to room temperature. After *ca.* 16 h the reaction mixture was concentrated under reduced pressure using a dry ice trap. The residue was triturated with hexane (10 mL) and the solution was carefully decanted from precipitates using a syringe into a separate 100 mL Kugelrohr flask (3x). The hexane washings were concentrated under reduced pressure using a dry ice trap and the residue was heated at 75 °C *in vacuo* (1 Torr) for *ca.* 3 h to remove the excess of iPr_2SiCl_2 . The crude monochlorosilane was cooled to 0 °C and imidazole (0.340 g, 5.00 mmol) in DCM (2 mL with washings) was added, followed by alcohol **64** (0.286 g, 0.840 mmol) in DCM (3 mL with washings) and the reaction was warmed to room temperature. After 15 h (TLC control) the reaction mixture was quenched with saturated aqueous NH_4Cl and

partitioned between Et₂O and water. Phases were separated and the aqueous layer was washed with Et₂O (2x). The combined organic layers were washed with water (2x), brine, dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (silica gel, Et₂O/petroleum ether – 1:22, 1:20) afforded the mixed silaketal **80** (0.6342 g, 0.705 mmol, 84% yield) as colourless oil.

R_f = 0.53 (Et₂O/hexanes – 1:3).

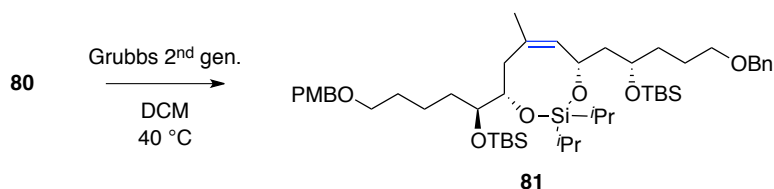
$[\alpha]_{\text{D}}^{20}$ –4.9 (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.38-7.36 (m, 5H), 7.34-7.30 (m, 2H), 6.92-6.91 (m, 2H), 5.86 (ddd, *J* = 17.2, 10.3, 7.0 Hz, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 5.14 (d, *J* = 10.2 Hz, 1H), 4.83 (s, 2H), 4.54 (s, 2H), 4.50 (d, A of AB, *J*_{AB} = 11.4 Hz, 1H), 4.50-4.46 (m, 1H), 4.47 (d, B of AB, *J*_{AB} = 11.5 Hz, 1H), 4.05 (ddd, *J* = 7.0, 3.8, 2.2 Hz, 1H), 3.82 (s, 3H), 3.82-3.77 (m, 2H), 3.51 (app. t, *J* = 6.3 Hz, 4H), 2.44 (d, A of AB, *J*_{AB} = 13.2 Hz, 1H), 2.09 (dd, B of ABX, *J*_{AB} = 13.6 Hz, *J*_{BX} = 9.5 Hz, 1H), 1.93 (ddd, A of ABXY, *J*_{AB} = 13.4 Hz, *J*_{AX} = 8.6 Hz, *J*_{AY} = 4.8 Hz, 1H), 1.81 (s, 3H), 1.75-1.55 (m, 9H), 1.38-1.26 (m, 2H), 1.11-0.98 (m, 14H), 0.96 (s, 9H), 0.95 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 159.11 (e), 143.48 (e), 141.25 (o), 138.68 (e), 130.88 (e), 129.20 (o), 128.38 (o), 127.60 (o), 127.53 (o), 114.83 (e), 113.74 (o), 112.92 (e), 74.94 (o), 73.46 (o), 72.85 (e), 72.55 (e), 71.43 (o), 70.59 (e), 70.23 (e), 68.96 (o), 55.20 (o), 45.63 (e), 39.16 (e), 34.42 (e), 30.16 (e), 29.80 (e), 25.99 (o), 24.97 (e), 23.49 (e), 23.06 (o), 18.09 (e), 18.07 (e), 17.74 (o), 17.69 (o), 17.62 (o), 17.58 (o), 13.22 (o), 12.97 (o), –3.80 (o), –3.90 (o), –4.28 (o), –4.38 (o).

IR (Neat) 2947 (m), 2929 (m), 2857 (m), 1646 (w), 1614 (w), 1513 (w), 1098 (s) cm^{–1}.

HRMS (ESI, [M+Na]⁺) calcd for C₅₁H₉₀O₇NaSi₃ 921.5892, found 921.5909.



(4*S*,8*S*,*Z*)-8-((*S*)-5-(Benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)pentyl)-4-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)pentyl)-2,2-diisopropyl-6-methyl-5,8-dihydro-4*H*-1,3,2-dioxasilocine (81)

To a solution of **80** (1.0 g, 1.11 mmol) in DCM (102 mL) was added Grubbs 2nd generation catalyst (0.142 g, 0.167 mmol) in DCM (4 mL) and the reaction mixture was refluxed for *ca.* 24 hours. After that time a second portion of Grubbs 2nd generation catalyst (0.142 g, 0.167 mmol) in DCM (4 mL) was added and the mixture was refluxed for *ca.* 48 hours (TLC control), before it was cooled to room temperature and treated with DMSO (2.37 mL, 33.4 mmol). After *ca.* 16 hours the reaction was concentrated *in vacuo* and passed through a pad of silica gel (washed with Et₂O/petroleum ether 1:5). The solution was concentrated *in vacuo* and the crude product was purified by flash chromatography (silica gel, Et₂O/hexanes – 1:20) to afford the cyclic silaketal **81** (0.94 g, 1.08 mmol, 97% yield) as a colourless oil.

R_f = 0.74 (Et₂O/hexanes – 1:2).

$[\alpha]_{\text{D}}^{20} +1.4$ (*c* 0.5, CHCl₃).

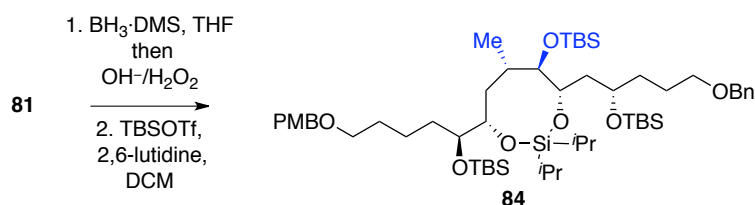
¹H NMR (500 MHz, CDCl₃) δ 7.34-7.31 (m, 4H), 7.29-7.25 (m, 3H), 6.89-6.85 (m, 2H), 5.56 (dd, *J* = 5.9, 1.1 Hz, 1H), 4.50 (s, 2H), 4.45 (d, A of AB, *J*_{AB} = 11.7 Hz, 1H), 4.42 (d, B of AB, *J*_{AB} = 11.7 Hz, 1H), 4.40 (quintet, *J* = 4.9 Hz, 1H), 3.94 (septet, *J* = 3.9 Hz, 1H), 3.90 (ddd, *J* = 9.7, 3.7, 1.4 Hz, 1H), 3.80 (s, 3H), 3.62 (quintet, *J* = 3.9 Hz, 1H), 3.51-3.42 (m, 4H), 2.80 (dd, A of ABX, *J*_{AB} = 13.5 Hz, *J*_{AX} = 9.8 Hz, 1H), 1.99 (d, A of AB, *J*_{AB} = 12.8 Hz, 1H), 1.86 (ddd, B of ABXY, *J*_{AB} = 13.7 Hz, *J*_{BX} = 9.5 Hz, *J*_{BY} = 4.4 Hz, 1H), 1.76-1.68 (m, 2H), 1.72 (s, 3H), 1.67-1.55

(m, 5H), 1.54-1.41 (m, 2H), 1.35-1.25 (m, 2H), 1.07-1.00 (m, 1H), 0.99 (s, 3H), 0.98 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.94-0.84 (m, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 159.07 (e), 138.71 (e), 136.31 (e), 131.00 (o), 130.80 (e), 129.21 (o), 128.32 (o), 127.57 (o), 127.44 (o), 113.73 (o), 75.61 (o), 75.44 (o), 72.76 (e), 72.57 (e), 70.76 (e), 70.19 (e), 69.52 (o), 68.64 (o), 55.28 (o), 45.69 (e), 35.12 (e), 32.61 (e), 30.90 (e), 30.03 (e), 25.97 (o), 25.93 (o), 25.56 (e), 25.53 (o), 23.00 (e), 18.11 (e), 18.05 (e), 17.82 (o), 17.79 (o), 17.63 (o), 17.60 (o), 13.45 (o), 13.07 (o), -4.22 (o), -4.31 (o), -4.49 (o), -4.52 (o).

IR (Neat) 2929 (m), 2857 (m), 1729 (w), 1613 (w), 1513 (w), 1097 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{49}\text{H}_{86}\text{O}_8\text{NaSi}_3$ 893.5579, found 893.5598.



(4*S*,5*R*,6*S*,8*S*)-4-((*S*)-5-(Benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)pentyl)-5-((*tert*-butyldimethylsilyl)oxy)-8-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)pentyl)-2,2-diisopropyl-6-methyl-1,3,2-dioxasilocane (84)

To a solution of **81** (0.516 g, 0.592 mmol) in THF (3 mL) was added borane-tetrahydrofuran complex (3.0 mL, 1.0 M in THF, 3 mmol) and the reaction mixture was stirred for *ca.* 2 h (TLC control), before it was cooled to 0 °C and quenched with 0.1 mL of MeOH, followed by a careful dropwise addition of the premixed cold solution of sodium hydroxide (4.9 mL, 14.80 mmol) and hydrogen peroxide (1.51 mL, 14.80 mmol). The resulting mixture was vigorously stirred at room temperature for *ca.* 16 h and then partitioned between water and DCM. Phases were

separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to afford crude alcohol, which was used in the next step without purification.

A solution of crude alcohol intermediate (~0.592 mmol) in DCM (2 mL) was treated sequentially with 2,6-lutidine (0.69 mL, 5.92 mmol) and TBSOTf (0.82 mL, 3.55 mmol) at 0 °C. After 40 min (TLC control) the reaction was quenched with saturated aqueous NaHCO₃ and partitioned between water and Et₂O. Phases were separated and the aqueous layer was washed with Et₂O (2x). The combined organic layers were washed with water, brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et₂O/hexanes – 1:20) afforded the TBS ether **84** (0.425 g, 0.424 mmol, 72% yield over 2 steps) as a colourless oil.

R_f = 0.56 (Et₂O/hexanes – 1:5).

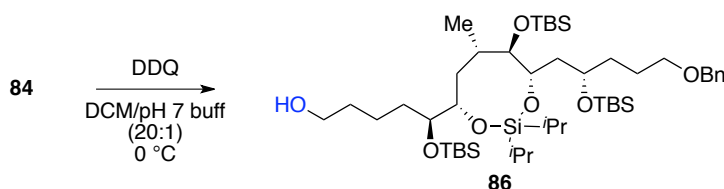
$[\alpha]_{\text{D}}^{20}$ –5.5 (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, C₆D₆) δ 7.33-7.31 (m, 2H), 7.27-7.26 (m, 2H), 7.21-7.18 (m, 2H), 7.11-7.09 (m, 1H), 6.84-6.81 (m, 2H), 4.38 (d, A of AB, *J*_{AB} = 11.9 Hz, 1H), 4.33 (d, B of AB, *J*_{AB} = 10.9 Hz, 1H), 4.35 (s, 2H), 4.26 (app. qd, *J* = 6.4, 3.1 Hz, 1H), 4.21 (dd, A of ABX, *J*_{AB} = 5.4 Hz, *J*_{AX} = 3.1 Hz, 1H), 4.17 (dd, *J* = 9.8, 3.8 Hz, 1H), 4.08 (app. dt, B of ABX₂, *J*_{AB} = 6.4 Hz, *J*_{BX} = 5.3 Hz, 1H), 3.74 (app. dt, *J* = 8.1, 4.0 Hz, 1H), 3.44-3.35 (m, 4H), 3.30 (s, 3H), 2.19-2.08 (m, 2H), 2.11 (app. dt, A of ABX₂, *J*_{AB} = 14.3 Hz, *J*_{BX} = 7.2 Hz, 1H), 1.97 (ddd, B of ABXY, *J*_{AB} = 14.1 Hz, *J*_{BX} = 7.2 Hz, *J*_{BY} = 5.0 Hz, 1H), 1.93-1.84 (m, 4H), 1.77-1.63 (m, 4H), 1.57 (app. dt, B of ABX₂, *J*_{AB} = 14.5 Hz, *J*_{BX} = 9.9 Hz, 1H), 1.59-1.43 (m, 2H), 1.24 (d, *J* = 6.1 Hz, 3H), 1.23 (d, *J* = 7.3 Hz, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.20-1.14 (m, 1H), 1.13-1.08 (m, 1H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.05 (s, 9H), 1.04 (s, 9H), 1.00 (s, 9H), 0.25 (s, 3H), 0.23 (s, 3H), 0.22 (s, 3H), 0.19 (s, 3H), 0.10 (s, 3H), 0.10 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 159.64 (e), 139.53 (e), 131.56 (e), 129.27 (o), 128.51 (o), 127.67 (o), 127.55 (o), 114.05 (o), 77.94 (o), 76.21 (o), 75.49 (o), 72.96 (e), 72.78 (e), 71.92 (o), 70.78 (e), 70.18 (e), 70.10 (o), 54.79 (o), 43.71 (e), 37.07 (e), 34.80 (o), 33.90 (e), 31.39 (e), 30.63 (e), 26.35 (o), 26.32 (o), 26.22 (o), 25.43 (e), 23.50 (e), 18.45 (e), 18.44 (e), 18.41 (e), 18.12 (o), 18.07 (o), 17.79 (o), 17.71 (o), 16.43 (o), 14.10 (o), 13.78 (o), -3.53 (o), -3.64 (o), -3.68 (o), -4.05 (o), -4.22 (o).

IR (Neat) 2951 (m), 2928 (m), 2856 (m), 1613 (w), 1587 (w), 1513 (w), 1463 (m), 1248 (s), 1100 (s), 1075 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{55}\text{H}_{102}\text{O}_7\text{NaSi}_8$ 1025.6550, found 1025.6556.



(4*S*,5*R*,6*S*,8*S*)-4-((*S*)-5-(Benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)pentyl)-5-((*tert*-butyldimethylsilyl)oxy)-8-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)-5-(phenylsulfonyl)pentyl)-2,2-diisopropyl-6-methyl-1,3,2-dioxasilocane (85)

To a solution of **84** (0.453 g, 0.451 mmol) in a 20:1 mixture DCM (2 mL) and phosphate 7.0 buffer (0.1 mL) at 0 °C was added DDQ (0.164 g, 0.721 mmol) and the reaction stirred at that temp for *ca.* 2 h, before it was quenched with saturated aqueous NaHCO_3 and partitioned between water and DCM. Phases were separated and aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , $\text{Et}_2\text{O}/\text{PhMe}$ – 1:50, 1:40, 1:30) furnished alcohol **86** (0.389 g, 0.440 mmol, 98% yield) as a colourless oil.

R_f = 0.14 ($\text{Et}_2\text{O}/\text{hexanes}$ – 1:5).

Chapter 4

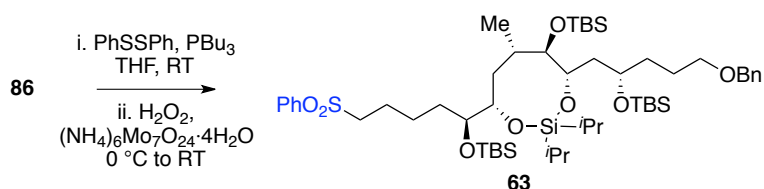
$[\alpha]_{\text{D}}^{20} -4.6$ (c 0.5, CHCl_3).

^1H NMR (500 MHz, CDCl_3) δ 7.53-7.51 (m, 2H), 7.42-7.39 (m, 2H), 7.32-7.29 (m, 1H), 4.56 (s, 2H), 4.45 (app. qd, $J = 6.4, 3.3$ Hz, 1H), 4.41 (d, A of ABX, $J_{AB} = 5.4$ Hz, $J_{AX} = 3.2$ Hz, 1H), 4.36 (dd, $J = 9.8, 3.8$ Hz, 1H), 4.29 (app. dt, $J = 6.4, 5.3$ Hz, 1H), 3.92 (app. dt, $J = 8.1, 4.0$ Hz, 1H), 3.62-3.59 (m, 4H), 2.39-2.27 (m, 2H), 2.30 (dd, A of ABX, $J_{AB} = 15.6$ Hz, $J_{AX} = 6.7$ Hz, 1H), 2.17 (ddd, A of ABXY, $J_{AB} = 14.0$ Hz, $J_{AX} = 7.1$ Hz, $J_{AY} = 5.0$ Hz, 1H), 2.13-2.03 (m, 4H), 1.89-1.83 (m, 1H), 1.79-1.61 (m, 5H), 1.76 (app. dt, B of ABX, $J_{AB} = 14.8$ Hz, $J_{BX} = 10.0$ Hz, 1H), 1.59-1.52 (m, 1H), 1.44 (d, $J = 7.2$ Hz, 3H), 1.43 (d, $J = 7.4$ Hz, 3H), 1.42 (s, 3H), 1.41 (d, $J = 5.4$ Hz, 3H), 1.40-1.33 (m, 1H), 1.31-1.28 (d, $J = 6.5$ Hz, 3H), 1.26 (s, 9H), 1.24 (s, 9H), 1.20 (s, 9H), 0.45 (s, 3H), 0.43 (s, 3H), 0.42 (s, 3H), 0.40 (s, 3H), 0.31 (s, 3H), 0.30 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 140.07 (e), 129.09 (o), 128.25 (o), 128.14 (o), 78.54 (o), 76.73 (o), 76.02 (o), 73.52 (e), 72.45 (o), 71.34 (e), 70.66 (o), 63.19 (e), 44.30 (e), 37.61 (e), 35.37 (o), 34.48 (e), 33.99 (e), 31.86 (e), 26.89 (o), 26.86 (o), 26.74 (o), 26.01 (e), 23.47 (e), 19.00 (e), 18.99 (e), 18.96 (e), 18.67 (o), 18.62 (o), 18.33 (o), 18.26 (o), 16.98 (o), 14.67 (o), 14.34 (o), -2.99 (o), -3.08 (o), -3.13 (o), -3.51 (o), -3.69 (o).

IR (Neat) 3337 (br), 2947 (m), 2929 (m), 2857 (m), 1463 (w), 1251 (m), 1099 (m), 1067 (m) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{47}\text{H}_{94}\text{O}_7\text{NaSi}_4$ 905.5974, found 905.5984.



(4*S*,5*R*,6*S*,8*S*)-4-((*S*)-5-(Benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)pentyl)-5-((*tert*-butyldimethylsilyl)oxy)-8-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)-5-(phenylsulfonyl)pentyl)-2,2-diisopropyl-6-methyl-1,3,2-dioxasilocane (63)

To a solution of **86** (0.341 g, 0.386 mmol) and PhSSPh (0.337 g, 1.543 mmol) in THF (2 mL) was added tributylphosphine (0.39 mL, 1.543 mmol) and the reaction mixture was stirred for *ca.* 1 h (TLC control). The reaction was then cooled to 0 °C and treated sequentially with 30% aqueous hydrogen peroxide (0.94 mL, 9.26 mmol) and ammonium molybdate tetrahydrate (0.119 g, 0.096 mmol). The reaction mixture was warmed to room temperature and stirred for *ca.* 16 h (TLC control), before it was quenched with aqueous NaHCO₃ and partitioned between water and DCM. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et₂O/PhMe – 1:80, 1:60) furnished **63** (0.298 g, 0.296 mmol, 77% yield) as a colourless oil.

$R_f = 0.14$ (Et₂O/hexanes – 1:5).

$[\alpha]_D^{20} -3.6$ (*c* 0.5, CHCl₃).

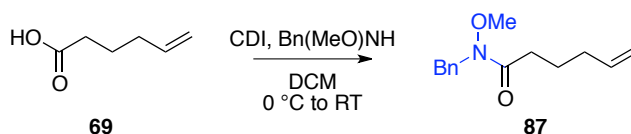
¹H NMR (500 MHz, C₆D₆) δ 7.79-7.75 (m, 2H), 7.30-7.28 (m, 2H), 7.20-7.17 (m, 2H), 7.11-7.08 (m, 1H), 7.01-6.93 (m, 3H), 4.35 (d, A of AB, $J_{AB} = 12.4$ Hz, 1H), 4.33 (d, B of AB, $J_{AB} = 12.5$ Hz, 1H), 4.20 (app. qd, $J = 6.3, 3.4$ Hz, 1H), 4.13 (d, A of ABX, $J_{AB} = 5.5$ Hz, $J_{AX} = 3.2$ Hz, 1H), 4.06-4.01 (m, 2H), 3.57 (app. dt, $J = 7.2, 4.7$ Hz, 1H), 3.38 (t, $J = 6.1$ Hz, 2H), 2.76 (app. dt, A of ABX₂, $J_{AB} = 14.5$ Hz, $J_{AX} = 7.8$ Hz, 1H), 2.73 (app. dt, B of ABX₂, $J_{AB} = 14.7$ Hz, $J_{BX} = 7.8$ Hz, 1H), 2.14-2.09

(m, 1H), 2.07 (app. dt, A of ABX₂, $J_{AB} = 13.9$ Hz, $J_{AX} = 6.9$ Hz, 1H), 1.99 (app. dt, B of ABX, $J_{AB} = 14.9$ Hz, $J_{BX} = 7.0$ Hz, 1H), 1.91 (ddd, B of ABXY, $J_{AB} = 14.0$ Hz, $J_{BX} = 7.0$ Hz, $J_{BY} = 5.1$ Hz, 1H), 1.88-1.78 (m, 3H), 1.68-1.59 (m, 4H), 1.42 (app. dt, $J = 14.9$, 10.0 Hz, 1H), 1.37-1.23 (m, 3H), 1.16 (d, $J = 7.1$ Hz, 3H), 1.15 (d, $J = 7.2$ Hz, 3H), 1.14 (d, $J = 7.4$ Hz, 3H), 1.13 (d, $J = 7.5$ Hz, 3H), 1.10-1.04 (m, 2H), 1.05 (d, $J = 6.6$ Hz, 3H), 1.02 (s, 9H), 1.00 (s, 9H), 0.94 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H), 0.19 (s, 3H), 0.16 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H).

¹³C NMR (125 MHz, C₆D₆) δ 141.20 (e), 140.08 (e), 133.64 (o), 129.69 (o), 129.08 (o), 128.90 (o), 128.23 (o), 128.13 (o), 78.53 (o), 76.23 (o), 75.85 (o), 73.51 (e), 72.35 (o), 71.32 (e), 70.63 (o), 56.92 (e), 44.30 (e), 37.38 (e), 35.27 (o), 34.48 (e), 31.25 (e), 26.88 (o), 26.87 (o), 26.70 (o), 25.96 (e), 25.91 (e), 23.89 (e), 18.99 (e), 18.89 (e), 18.64 (o), 18.59 (o), 18.31 (o), 18.22 (o), 16.96 (o), 14.59 (o), 14.24 (o), -3.01 (o), -3.07 (o), -3.13 (o), -3.50 (o), -3.71 (o), -3.74 (o).

IR (Neat) 2951 (m), 2929 (m), 2857 (m), 1463 (w), 1251 (m), 1149 (m), 1087 (s), 834 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₅₃H₉₈O₈NaSi₄S 1029.5957, found 1029.5956.



***N*-Benzyl-*N*-methoxyhex-5-enamide (87)**

To a solution of CDI (2.48 g, 15.27 mmol) in DCM (40 mL) at 0 °C was added hex-5-enoic acid (1.45 g, 12.73 mmol). The reaction warmed to room temperature and stirred for *ca.* 2.5 h (TLC control). *N*-benzyl-*O*-methylhydroxylamine (8.32 g, 15.27 mmol) in DCM (5 mL with washings) was added and the reaction mixture was stirred for *ca.* 16 h (TLC control), before it was quenched with saturated aqueous

NH₄Cl and partitioned between water and Et₂O. Phases were separated and the aqueous layer was washed with Et₂O (2x). The combined organic layers were dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (silica gel, Et₂O/hexanes – 1:1) afforded amide **87** (2.75 g, 11.77 mmol, 92% yield) as a colourless oil.

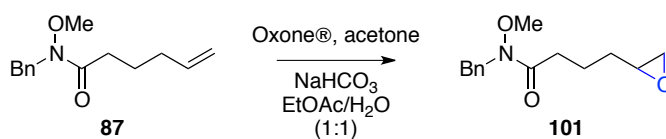
R_f = 0.19 (Et₂O/hexanes – 1:1).

¹H NMR (500 MHz, CDCl₃) δ 7.29-7.23 (m, 5H), 5.75 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 4.98 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.93 (ddt, *J* = 10.2, 2.1, 1.1 Hz, 1H), 4.73 (s, 2H), 3.56 (s, 3H), 2.43 (t, *J* = 7.5 Hz, 2H), 2.07 (app. ddt, *J* = 14.4, 7.1, 1.2 Hz, 2H), 1.72 (quintet, *J* = 7.5 Hz, 2H),

¹³C NMR (125 MHz, CDCl₃) δ 138.15 (o), 136.68 (e), 128.57 (o), 128.38 (o), 127.64 (o), 115.18 (e), 49.03 (e), 62.15 (o), 33.33 (e), 31.42 (e), 23.68 (e).

IR (Neat) 3066 (w), 3033 (w), 2937 (w), 1659 (vs), 1605 (w), 1440 (m), 1401 (s) cm⁻¹.

HRMS (CI, [M+NH₄]⁺) calcd for C₁₄H₂₀O₂N 234.1489, found 234.1487.



N-Benzyl-N-methoxy-4-(oxiran-2-yl)butanamide (100)

To a solution of **87** (2.75 g, 11.77 mmol) in a mixture of EtOAc (59 mL), water (59 mL) and acetone (17 mL, 235 mmol) was added NaHCO₃ (9.88 g, 118 mmol). The resulting suspension was vigorously stirred while an aqueous solution (200 mL) of Oxone® (28.9 g, 47.1 mmol) was added dropwise over *ca.* 3 h (TLC control). After that time an additional NaHCO₃ (4.94 g, 59 mmol) and acetone (8.5 mL, 117.5 mmol) were added, followed by a portionwise solid Oxone® (7.0 g, 11.39 mmol).

After *ca.* 1 h (TLC control) the reaction mixture was partitioned between water and EtOAc. Phases were separated and the aqueous layer was washed with EtOAc (3x). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et₂O/hexanes – 2:1, 3:1) afforded epoxide **101** (2.87 g, 11.50 mmol, 98% yield) as a colourless oil.

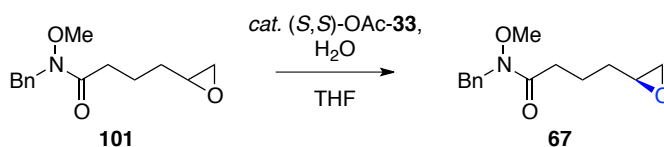
R_f = 0.35 (EtOAc/hexanes – 1:1).

¹H NMR (500 MHz, CDCl₃) δ 7.30-7.21 (m, 5H), 4.73 (s, 2H), 3.57 (s, 3H), 2.87 (app. ddt, J = 6.4, 4.2, 2.6 Hz, 1H), 2.68 (app. t, A of AM₂, J_{AM} = 4.5 Hz, 1H), 2.51 (app. dt, A of ABX₂, J_{AB} = 16.8 Hz, J_{AX} = 7.4 Hz, 1H), 2.47 (app. dt, B of ABX₂, J_{AB} = 16.8 Hz, J_{BX} = 7.4 Hz, 1H), 2.41 (dd, M of AMX, J_{AM} = 5.0 Hz, J_{MX} = 2.7 Hz, 1H), 1.81 (app. d of quintets, A of ABX₄, J_{AB} = 16.1 Hz, J_{AX} = 7.6 Hz, 1H), 1.77 (app. d of quintets, B of ABX₄, J_{AB} = 16.3 Hz, J_{BX} = 7.5 Hz, 1H), 1.60 (dddd, A of ABXYZ, J_{AB} = 13.8 Hz, J_{AX} = 8.6 Hz, J_{AY} = 6.6 Hz, J_{AZ} = 5.0 Hz, 1H), 1.50 (app. td, B of A₂BX, J_{AB} = 14.3 Hz, J_{BX} = 7.2 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 174.18 (e), 136.63 (e), 128.59 (o), 128.41 (o), 127.68 (o), 62.17 (o), 52.06 (o), 49.13 (e), 46.88 (e), 32.03 (e), 31.70 (e), 21.09 (e).

IR (Neat) 3484 (br), 2938 (w), 1655 (vs), 1605 (w), 1445 (m), 1404 (s) cm⁻¹.

HRMS (CI, [M+H]⁺) calcd for C₁₄H₂₀O₃N 250.1438, found 250.1437.



(*S*)-*N*-Benzyl-*N*-methoxy-4-(oxiran-2-yl)butanamide (**67**)

A solution of **101** (2.87 g, 11.50 mmol), (*S,S*)-Co-OAc-**33** (0.076 g, 0.115 mmol) and water (0.114 mL, 6.32 mmol) in THF (1 mL) was stirred for *ca.* 36 h (TLC control). The reaction mixture was directly purified by flash chromatography (silica gel,

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DCM/hexanes – 1:1, Et₂O/hexanes – 2:1, 3:1) to afford (*S*)-epoxide **67** (0.86 g, 3.46 mmol, 60% yield) as a brown oil.

Enantiomeric excess of **67** was determined by chiral HPLC analysis of was shown to be >99% *ee*. Chiral AS-H column, IPA/Hex – 3.0:97.0, 1.5 mL/min, 25 °C, 210 nm, *t_r*(minor) = 27.5 min, *t_r* (major) = 36.0 min.

R_f = 0.35 (EtOAc/hexanes – 1:1).

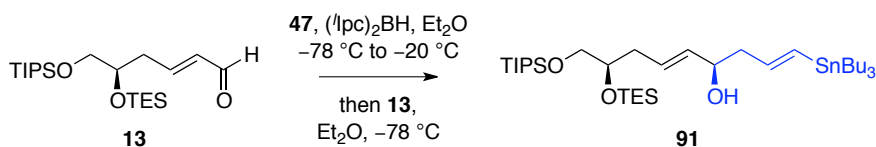
$[\alpha]_{\text{D}}^{20}$ –4.0 (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.29-7.21 (m, 5H), 4.73 (s, 2H), 3.57 (s, 3H), 2.87 (app. dt, *J* = 6.4, 4.3, 2.5 Hz, 1H), 2.68 (app. t, A of AM₂, *J_{AM}* = 4.5 Hz, 1H), 2.51 (app. dt, A of ABX₂, *J_{AB}* = 16.9 Hz, *J_{AX}* = 7.4 Hz, 1H), 2.47 (app. dt, B of ABX₂, *J_{AB}* = 17.0 Hz, *J_{BX}* = 7.3 Hz, 1H), 2.41 (dd, M of AMX, *J_{AM}* = 5.0 Hz, *J_{MX}* = 2.7 Hz, 1H), 1.80 (app. d of quintets, *J* = 16.1, 7.6 Hz, 1H), 1.77 (app. d of quintets, *J* = 16.3, 7.5 Hz, 1H), 1.60 (dddd, A of ABXYZ, *J_{AB}* = 13.8 Hz, *J_{AX}* = 8.6 Hz, *J_{AY}* = 6.6 Hz, *J_{AZ}* = 5.0 Hz, 1H), 1.50 (app. td, B of A₂BX, *J_{AB}* = 14.3 Hz, *J_{BX}* = 7.0 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 174.18 (e), 136.63 (e), 128.59 (o), 128.41 (o), 127.68 (o), 62.17 (o), 52.06 (o), 49.13 (e), 46.88 (e), 32.03 (e), 31.70 (e), 21.09 (e).

IR (Neat) 3033 (w), 2938 (w), 1655 (vs), 1605 (w), 1445 (m), 1404 (s) cm^{–1}.

HRMS (CI, [M+NH₄]⁺) calcd for C₁₄H₂₀O₃N 250.1438, found 250.1436.



(1*E*,4*R*,5*E*,8*R*)-1-(Tributylstannyl)-8-((triethylsilyl)oxy)-9-((triisopropylsilyl)oxy)nona-1,5-dien-4-ol (**91**)

A finely crushed (^{*i*}Ipc)₂BH (3.32 g, 11.58 mmol) was charged into a round bottom flask in a glove box. The flask was capped with a rubber septum and removed from

the glove box. Et₂O (45 mL) was added to the flask and the suspension was cooled to –40 °C. Allenylstannane **47** (5.5 mL, 90% w/w, 16.6 mmol) was added. This mixture was stirred for *ca.* 2 h at –40 °C and slowly warmed to –20 °C for *ca.* 3 h, during which time most of the borane dissolved. The reaction mixture was cooled to –78 °C and a solution of **13** (2.02 g, 5.04 mmol) in Et₂O (2 mL with washings) was added. The mixture was stirred for 16 h at that temperature (TLC control), before it was quenched with MeOH (0.25 mL) and the reaction was allowed to warm to 0 °C. A saturated aqueous NaHCO₃ (8.5 mL) was added, followed by slow addition of 30% H₂O₂ (16 mL). The reaction was stirred vigorously for *ca.* 16 h at that temperature, then diluted with brine and Et₂O. Phases were separated and the aqueous layer was washed with Et₂O (3x). The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, neutralised with 1% Et₃N in hexane, Et₂O/hexanes – 1:25, 1:20) afforded the vinyl stannane **91** (3.27 g, 4.47 mmol, 89% yield) as a colourless oil.

R_f = 0.12 (Et₂O/hexanes – 20:1).

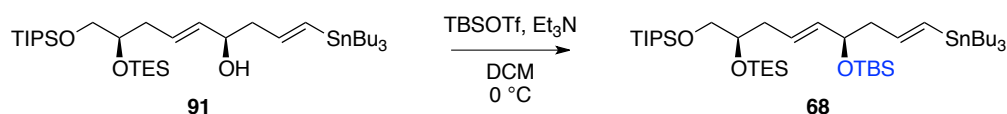
$[\alpha]_{\text{D}}^{20} +1.3$ (*c* 1.0, CH₂Cl₂).

¹H NMR (500 MHz, C₆D₆) δ 6.24-6.09 (m, 2H), 5.89 (dt, *J* = 15.0, 7.4 Hz, 1H), 5.68 (dd, *J* = 15.4, 6.1 Hz, 1H), 4.15 (quintet, *J* = 5.5 Hz, 1H), 3.88 (quintet, *J* = 5.7 Hz, 1H), 3.79 (dd, A of ABX, *J*_{AB} = 9.6 Hz, *J*_{AX} = 5.0 Hz, 1H), 3.67 (dd, B of ABX, *J*_{AB} = 9.6 Hz, *J*_{BX} = 6.8 Hz, 1H), 2.56 (app. dt, A of ABX₂, *J*_{AB} = 13.1 Hz, *J*_{AX} = 6.4 Hz, 1H), 2.50-2.42 (m, 2H), 2.38 (app. dt, B of ABX₂, *J*_{AB} = 13.9 Hz, *J*_{BX} = 7.0 Hz, 1H), 1.63-1.51 (m, 6H), 1.38 (sextet, *J* = 7.4 Hz, 6H), 1.36 (s, 1H), 1.15-1.06 (m, 21H), 1.04 (t, *J* = 8.0 Hz, 9H), 0.98-0.90 (m, 6H), 0.95 (t, *J* = 7.4 Hz, 9H), 0.66 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR (125 MHz, C_6D_6) δ 146.48 (o), 136.40 (o), 132.36 (o), 127.81 (o), 74.03 (o), 72.39 (o), 68.17 (e), 47.49 (e), 38.47 (e), 30.18 (e), 28.29 (e), 18.87 (o), 14.57 (o), 12.92 (o), 10.34 (e), 7.81 (o), 6.03 (e).

IR (Neat) 3433 (br), 2955 (m), 2923 (m), 1599 (w), 1463 (m), 1103 (m), 995 (m) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{36}\text{H}_{76}\text{O}_3\text{NaSi}_3^{120}\text{Sn}$ 755.4253, found 755.4260.



(5*R*,9*R*,*E*)-12,12-Diisopropyl-2,2,3,3,13-pentamethyl-5-((*E*)-3-(tributylstannyl)allyl)-9-((triethylsilyl)oxy)-4,11-dioxo-3,12-disilatetradec-6-ene (68)

A solution of **91** (3.57 g, 4.88 mmol) in DCM (20 mL) treated with triethylamine (2.72 mL, 19.50 mmol) and TBSOTf (1.68 mL, 7.31 mmol) at 0 °C. The reaction mixture stirred for *ca.* 30 min (TLC control), then quenched with saturated aqueous NaHCO_3 and partitioned between water and Et_2O . Phases were separated and the aqueous layer was washed with Et_2O (2x). The combined organic layers were washed with water, brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel deactivated with 1% Et_3N , Et_2O /hexanes – 0:100, 1:50) afforded the TBS ether **68** (3.92 g, 4.63 mmol, 95% yield) as a colourless oil.

R_f = 0.44 (Et_2O /hexanes – 1:50).

$[\alpha]_D^{20} +3.5$ (*c* 1.0, CH_2Cl_2).

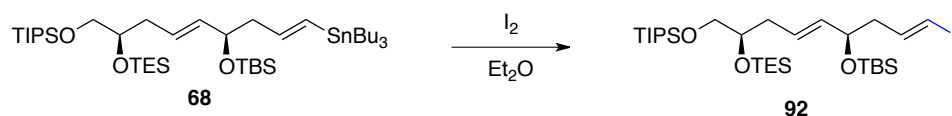
^1H NMR (500 MHz, CDCl_3) δ 6.32 (ddtd, $^3J_{(\text{Sn}, \text{H})} = 32.9$ Hz, $J_{(\text{H}, \text{H})} = 18.9, 6.3, 1.1$ Hz, 1H), 6.18 (ddd, $^2J_{(\text{Sn}, \text{H})} = 39.7$ Hz, $J_{(\text{H}, \text{H})} = 19.0, 1.0$ Hz, 1H), 5.90 (dt, $J = 15.0$,

7.4 Hz, 1H), 5.72 (dd, $J = 15.4, 6.2$ Hz, 1H), 4.28 (q, $J = 6.0$ Hz, 1H), 3.90 (quintet, $J = 5.5$ Hz, 1H), 3.78 (dd, A of ABX, $J_{AB} = 9.6$ Hz, $J_{AX} = 5.1$ Hz, 1H), 3.69 (dd, B of ABX, $J_{AB} = 9.6$ Hz, $J_{BX} = 6.8$ Hz, 1H), 2.59-2.46 (m, 3H), 2.40 (app. dt, B of ABX₂, $J_{AB} = 13.5$ Hz, $J_{BX} = 7.0$ Hz, 1H), 1.71-1.55 (m, 6H), 1.41 (quintet, $J = 7.4$ Hz, 6H), 1.17-1.09 (m, 21H), 1.06-1.03 (m, 9H), 1.05 (s, 9H), 1.02-0.99 (m, 6H), 0.96 (t, $J = 7.4$ Hz, 9H), 0.67 (q, $J = 8.0$ Hz, 6H), 0.15 (s, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 146.27 (o), 136.15 (o), 130.15 (o), 125.89 (o), 73.65 (o), 73.11 (o), 67.09 (e), 47.69 (e), 37.43 (e), 29.41 (e), 27.56 (e), 26.00 (o), 18.29 (e), 18.05 (o), 13.76 (o), 12.11 (o), 9.51 (e), 7.01 (o), 5.23 (e), -4.08 (o), -4.65 (o).

IR (Neat) 2955 (s), 2927 (s), 2868 (s), 1599 (w), 1463 (m), 1114 (s), 1069 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₄₂H₉₀O₃NaSi₃¹²⁰Sn 869.5118, found 869.5119.



(5*R*,9*R*,*E*)-5-((*E*)-3-Iodoallyl)-12,12-diisopropyl-2,2,3,3,13-pentamethyl-9-(((triethylsilyl)oxy)-4,11-dioxa-3,12-disilatetradec-6-ene (92)

To a cooled to 0 °C solution of **68** (1.754 g, 2.07 mmol) in Et₂O (20 mL) was added solid iodine (1.05 g, 4.15 mmol). After *ca.* 20 min (TLC control) the reaction mixture was quenched with saturated aqueous Na₂SO₃ and partitioned between water and DCM. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel deactivated with 1% Et₃N, Et₂O/hexanes – 0:100, 1:100) afforded the vinyl iodide **92** (1.398 g, 2.05 mmol, 99%) as a colourless oil.

R_f = 0.44 (Et₂O/hexanes – 1:50).

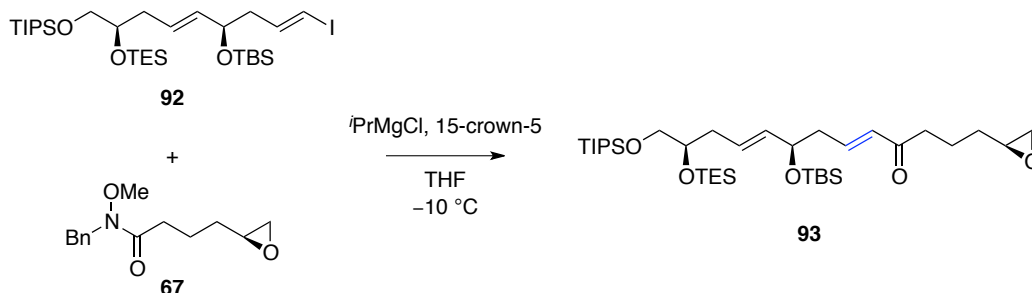
$[\alpha]_{\text{D}}^{20} -1.3$ (c 1.0, CH_2Cl_2).

^1H NMR (500 MHz, C_6D_6) δ 6.46 (dt, $J = 14.6, 7.4$ Hz, 1H), 5.82 (dtd, $J = 15.4, 7.7, 1.0$ Hz, 1H), 5.77 (dt, $J = 14.4, 1.2$ Hz, 1H), 5.49 (ddt, $J = 15.4, 6.1, 1.3$ Hz, 1H), 3.68 (q, $J = 5.9$ Hz, 1H), 3.86 (app. dq, $J = 6.9, 5.1$ Hz, 1H), 3.74 (dd, A of ABX, $J_{AB} = 9.6$ Hz, $J_{AX} = 5.2$ Hz, 1H), 3.64 (dd, B of ABX, $J_{AB} = 9.6$ Hz, $J_{BX} = 7.0$ Hz, 1H), 2.46 (app. dtd, A of ABX_2Y , $J_{AB} = 12.9$ Hz, $J_{AX} = 6.7$ Hz, $J_{AY} = 1.0$ Hz, 1H), 2.36 (app. dtd, B of ABX_2Y , $J_{AB} = 13.6$ Hz, $J_{BX} = 6.7$ Hz, $J_{BY} = 1.2$ Hz, 1H), 2.05 (app. dtd, A of ABX_2Y , $J_{AB} = 14.2$ Hz, $J_{AX} = 7.0$ Hz, $J_{AY} = 0.9$ Hz, 1H), 1.98 (dddd, B of ABXYZ , $J_{AB} = 14.0$ Hz, $J_{BX} = 7.1$ Hz, $J_{BY} = 2.1$ Hz, $J_{BZ} = 1.4$ Hz, 1H), 1.16-1.07 (m, 21H), 1.04 (q, $J = 7.0$ Hz, 9H), 0.97 (s, 9H), 0.65 (q, $J = 8.1$ Hz, 6H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 143.03 (o), 135.19 (o), 126.51 (o), 76.84 (o), 72.92 (o), 72.25 (o), 66.91 (e), 44.89 (e), 37.20 (e), 25.87 (o), 188.15 (e), 18.06 (o), 12.09 (o), 7.02 (o), 5.20 (e), -4.33 (o), -4.81 (o).

IR (Neat) 2950 (s), 2866 (s), 1607 (w), 1462 (m), 1116 (s), 1069 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{30}\text{H}_{63}\text{O}_3\text{NaSi}_3\text{I}$ 705.3028, found 705.3019.



(5*E*,8*R*,9*E*,12*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-1-((*S*)-oxiran-2-yl)-12-((triethylsilyl)oxy)-13-((triisopropylsilyl)oxy)trideca-5,9-dien-4-one (93)

Following the procedure of Knochel *et al.*^{42,43} modified by Castle,⁴⁴ a solution of **92** (0.548 g, 0.80 mmol) in THF (1.2 mL) was treated with $i\text{PrMgCl}\cdot\text{LiCl}$ complex (2.47

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mL, 1.055 M in THF, 2.61 mmol) at $-10\text{ }^{\circ}\text{C}$. The reaction mixture was warmed to room temperature and stirred for *ca.* 1.5 h, then cooled to $-20\text{ }^{\circ}\text{C}$ and epoxide **67** was added as a solution in THF (0.7 mL with washings). The reaction was warmed to $-10\text{ }^{\circ}\text{C}$ and stirred for *ca.* 2 h (TLC control), before it was quenched with saturated aqueous NH_4Cl and partitioned between water and DCM. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /hexanes – 1:12, 1:8) afforded enone **93** (0.1713 g, 0.256 mmol, 64% yield) as a colourless oil.

$R_f = 0.72$ (Et_2O /Hexanes – 2:1).

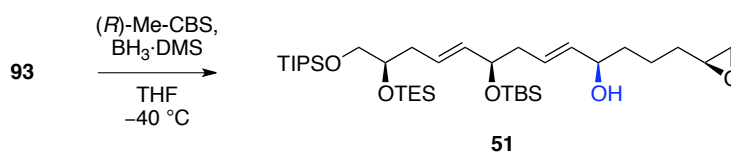
$[\alpha]_D^{20} +8.1$ (c 0.5, CHCl_3).

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 6.83 (dt, $J = 15.8, 7.4$ Hz, 1H), 6.10 (d, $J = 16.0$ Hz, 1H), 5.68 (dt, $J = 15.0, 7.4$ Hz, 1H), 5.48 (dd, $J = 15.4, 6.4$ Hz, 1H), 4.21 (q, $J = 6.1$ Hz, 1H), 3.72 (app. dq, $J = 7.0, 5.2$ Hz, 1H), 3.59 (dd, A of ABX, $J_{AB} = 9.6$ Hz, $J_{AX} = 5.1$ Hz, 1H), 3.47 (dd, B of ABX, $J_{AB} = 9.6$ Hz, $J_{BX} = 7.3$ Hz, 1H), 2.91 (dddd, $J = 6.3, 5.0, 3.8, 2.6$ Hz, 1H), 2.74 (dd, A of AMX, $J_{AM} = 4.8$ Hz, $J_{AX} = 4.1$ Hz, 1H), 2.62 (app. dt, A of ABX₂, $J_{AB} = 16.8$ Hz, $J_{AX} = 7.2$ Hz, 1H), 2.58 (app. dt, B of ABX₂, $J_{AB} = 16.8$ Hz, $J_{BX} = 7.2$ Hz, 1H), 2.47 (dd, M of AMX, $J_{AM} = 5.0$ Hz, $J_{MX} = 2.7$ Hz, 1H), 2.42-2.33 (m, 3H), 2.19 (app. dt, B of ABX₂, $J_{AB} = 13.7$ Hz, $J_{BX} = 6.8$ Hz, 1H), 1.80 (app. d of quintets, A of ABX₄, $J_{AB} = 16.0$ Hz, $J_{AX} = 7.4$ Hz, 1H), 1.77 (app. d of quintets, B of ABX₄, $J_{AB} = 15.8$ Hz, $J_{BX} = 7.4$ Hz, 1H), 1.61 (dddd, A of ABXYZ, $J_{AB} = 13.9$ Hz, $J_{AX} = 8.8$ Hz, $J_{AY} = 6.5$ Hz, $J_{AZ} = 5.0$ Hz, 1H), 1.52 (app. td, B of A₂BX, $J_{AB} = 14.2$ Hz, $J_{BX} = 7.1$ Hz, 1H), 1.12-0.99 (m, 21H), 0.95 (t, $J = 8.0$ Hz, 9H), 0.88 (s, 9H), 0.59 (q, $J = 7.8$ Hz, 6H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 199.92 (e), 144.24 (o), 134.98 (o), 132.42 (o), 127.25 (o), 72.83 (o), 72.66 (o), 66.90 (e), 52.16 (o), 47.01 (e), 41.90 (e), 39.21 (e), 37.21 (e), 32.07 (e), 25.97 (o), 20.64 (e), 18.31 (e), 18.15 (o), 12.09 (o), 7.03 (o), 5.12 (e), -4.05 (o), -4.67 (o).

IR (Neat) 2948 (m), 2866 (m), 1700 (w), 1676 (w), 1633 (w), 1067 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{36}\text{H}_{72}\text{O}_5\text{NaSi}_3$ 691.4585, found 691.4590.



(4*R*,5*E*,8*R*,9*E*,12*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-1-((*S*)-oxiran-2-yl)-12-((triethylsilyl)oxy)-13-((triisopropylsilyl)oxy)trideca-5,9-dien-4-ol (51**)**

To a cooled to $-40\text{ }^{\circ}\text{C}$ solution of enone **93** (0.1713 g, 0.256 mmol) and (*S*)-Me-CBS (0.256 mL, 1 M in PhMe, 0.256 mmol) in THF (1.5 mL) was added borane dimethylsulfide complex (0.181 mL, 1.792 mmol). The reaction mixture was stirred for *ca.* 16 h, before it was quenched with MeOH (0.1 mL) and partitioned between water and DCM. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /hexanes – 1:3, 1:2) afforded alcohol **51** (0.170 g, 0.253 mmol, 99% yield) as a colourless oil.

$R_f = 0.35$ (Et_2O /hexanes – 1:1).

$[\alpha]_{\text{D}}^{20} +3.4$ (*c* 1.0, CHCl_3).

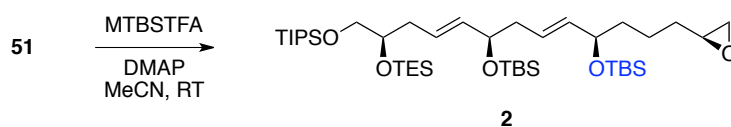
^1H NMR (500 MHz, CDCl_3) δ 5.65 (ddd, $J = 15.7, 7.3, 0.6$ Hz, 1H), 5.61 (ddd, $J = 15.7, 7.6, 0.9$ Hz, 1H), 5.49 (ddt, $J = 11.9, 7.1, 1.2$ Hz, 1H), 5.46 (ddt, $J = 13.8, 6.1, 1.3$ Hz, 1H), 4.09 (q, $J = 6.2$ Hz, 1H), 4.05 (q, $J = 6.4$ Hz, 1H), 3.72 (app. dq, $J = 6.5$,

5.3 Hz, 1H), 3.59 (dd, A of ABX, $J_{AB} = 9.7$ Hz, $J_{AX} = 5.3$ Hz, 1H), 3.52 (dd, B of ABX, $J_{AB} = 9.7$ Hz, $J_{BX} = 6.7$ Hz, 1H), 2.91 (app. tdd, $J = 5.3, 4.0, 2.7$ Hz, 1H), 2.74 (dd, A of ABX, $J_{AB} = 5.0$ Hz, $J_{AX} = 4.0$ Hz, 1H), 2.47 (dd, B of ABX, $J_{AB} = 5.0$ Hz, $J_{BX} = 2.7$ Hz, 1H), 2.33 (app. dt, A of ABX₂, $J_{AB} = 13.6$ Hz, $J_{AX} = 6.7$ Hz, 1H), 2.27-2.16 (m, 3H), 1.62-1.43 (m, 7H), 1.10-1.03 (m, 21H), 0.95 (t, $J = 8.0$ Hz, 9H), 0.88 (s, 9H), 0.60 (q, $J = 7.9$ Hz, 6H), 0.03 (s, 3H), 0.02 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 135.44 (o), 135.18 (o), 128.86 (o), 126.53 (o), 73.41 (o), 73.13 (o), 73.05 (o), 66.94 (e), 52.35 (o), 47.21 (e), 41.54 (e), 37.14 (e), 36.96 (e), 32.50 (e), 26.03 (o), 22.10 (e), 18.37 (e), 18.16 (o), 12.09 (o), 7.04 (o), 5.10 (e), -4.09 (o), -4.58 (o).

IR (Neat) 3441 (br), 2929 (s), 2866 (s), 1462 (m), 1412 (w), 1113 (s), 1097 (s), 1167 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₃₆H₇₄O₅NaSi₃ 693.4742, found 693.4745.



(5*R*,6*E*,9*R*,10*E*,13*R*)-9-((*tert*-Butyldimethylsilyl)oxy)-16,16-diisopropyl-2,2,3,3,17-pentamethyl-5-(3-((*S*)-oxiran-2-yl)propyl)-13-((triethylsilyl)oxy)-4,15-dioxa-3,16-disilaoctadeca-6,10-diene (2)

51 (0.0713 g, 0.106 mmol) was dissolved in MeCN (0.15 mL) and treated with MTBSTFA (0.256 g, 1.062 mmol) and DMAP (0.065 g, 0.531 mmol). After *ca.* 3 h (TLC control) the reaction mixture was directly purified by flash chromatography (silica gel, Et₂O/hexanes – 1:30) to afforded TBS ether **2** (0.0825 g, 0.105 mmol, 99% yield) as a colourless oil.

R_f = 0.77 (Et₂O/hexanes – 1:2).

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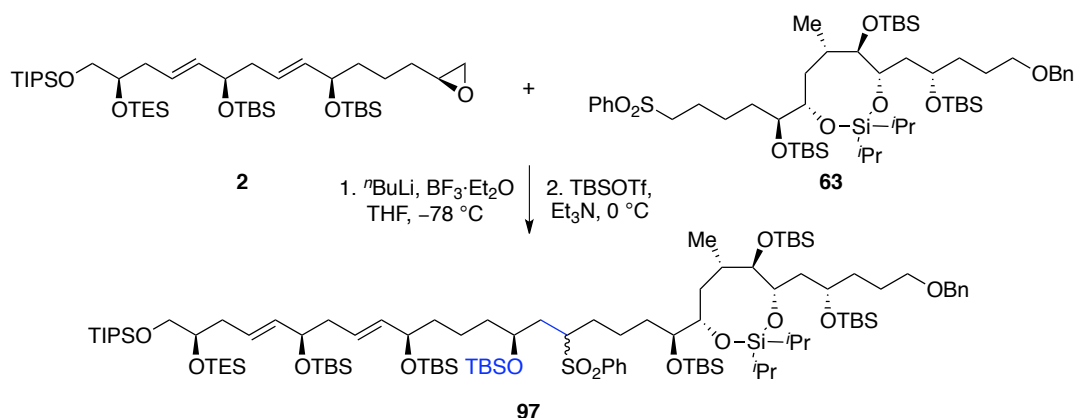
$[\alpha]_{\text{D}}^{20} +7.9$ (c 1.0, CHCl_3).

^1H NMR (500 MHz, CDCl_3) δ 5.62 (dt, $J = 14.9, 7.3$ Hz, 1H), 5.58 (dt, $J = 14.9, 7.3$ Hz, 1H), 5.47 (dd, $J = 15.4, 6.4$ Hz, 1H), 5.41 (dd, $J = 15.4, 6.6$ Hz, 1H), 4.08 (q, $J = 5.9$ Hz, 1H), 4.05 (q, $J = 6.0$ Hz, 1H), 3.71 (app. dq, $J = 6.6, 5.3$ Hz, 1H), 3.59 (dd, A of ABX, $J_{AB} = 9.6$ Hz, $J_{AX} = 5.2$ Hz, 1H), 3.49 (dd, B of ABX, $J_{AB} = 9.7$ Hz, $J_{BX} = 6.9$ Hz, 1H), 2.91-2.87 (m, 1H), 2.74 (dd, A of ABX, $J_{AB} = 4.9$ Hz, $J_{AX} = 4.1$ Hz, 1H), 2.45 (dd, B of ABX, $J_{AB} = 5.0$ Hz, $J_{BX} = 2.7$ Hz, 1H), 2.35 (app. dt, A of ABX_2 , $J_{AB} = 13.2$ Hz, $J_{AX} = 6.4$ Hz, 1H), 2.34-2.14 (m, 3H), 1.58-1.40 (m, 6H), 1.12-1.00 (m, 21H), 0.96 (t, $J = 8.0$ Hz, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.60 (q, $J = 7.9$ Hz, 6H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 135.70 (o), 135.56 (o), 126.66 (o), 126.35 (o), 73.60 (o), 73.54 (o), 73.04 (o), 67.04 (e), 52.45 (o), 47.26 (e), 41.82 (e), 38.31 (e), 37.40 (e), 32.63 (e), 26.07 (o), 21.85 (e), 18.37 (e), 18.16 (o), 12.09 (o), 7.05 (o), 5.11 (e), -3.96 (o), -4.06 (o), -4.60 (o), -4.63 (o).

IR (Neat) 2947 (s), 2928 (s), 2864 (s), 1463 (m), 1069 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{42}\text{H}_{88}\text{O}_5\text{NaSi}_4$ 807.5607, found 807.5618.



(4*S*,5*R*,6*S*,8*S*)-4-((*S*)-5-(Benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)pentyl)-5-((*tert*-butyldimethylsilyl)oxy)-2,2-diisopropyl-6-methyl-8-

((5*S*,11*S*,15*R*,16*E*,19*R*,20*E*,23*R*)-11,15,19-tris((*tert*-butyldimethylsilyl)oxy)-26,26-diisopropyl-2,2,3,3,27-pentamethyl-9-(phenylsulfonyl)-23-((triethylsilyl)oxy)-4,25-dioxo-3,26-disilaooctacos-16,20-dien-5-yl)-1,3,2-dioxasilocane (97)

To a cooled to $-78\text{ }^{\circ}\text{C}$ solution of sulfone **63** (0.129 g, 0.128 mmol) in THF (0.3 mL) was added $n\text{-BuLi}$ (0.080 mL, 1.6 M in hexanes, 0.128 mmol). After *ca.* 15 min the resulting yellow mixture was treated with a solution of epoxide **2** (0.050 g, 0.064 mmol) in THF (0.3 mL with washings), followed by $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.020 mL, 48% w/w, 0.077 mmol). The reaction mixture was stirred for *ca.* 30 min (TLC control), before it was quenched with RM saturated aqueous NH_4Cl and partitioned between water and DCM. Phases were separated and aqueous was washed with DCM (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo* to afford crude oil, which was used in the next step without purification.

The crude hydroxyl sulfone product (~ 0.064 mmol) was dissolved in DCM (0.85 mL) and treated with triethylamine (0.053 mL, 0.384 mmol) and TBSOTf (0.073 mL, 0.320 mmol) at $0\text{ }^{\circ}\text{C}$. After *ca.* 10 min (TLC control) the reaction was quenched with saturated aqueous NaHCO_3 and partitioned between water and Et_2O . Phases were separated and aqueous was washed with Et_2O (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /hexanes – 1:30, 1:22, 1:10, 1:5) afforded alcohol the TBS ether **97** (0.11 g, 0.058 mmol, 90% yield) as a colourless oil, together with the recovered sulfone **63** (0.056 g, 0.0556 mmol, 87%).

$R_f = 0.42$ (Et_2O /hexanes – 1:7).

$[\alpha]_D^{20} +5.9$ (c 0.47, CHCl_3).

The presence of diastereoisomers complicated the NMR analysis. The ^1H data of the major diastereoisomer is presented, while all observed ^{13}C peaks are outlined.

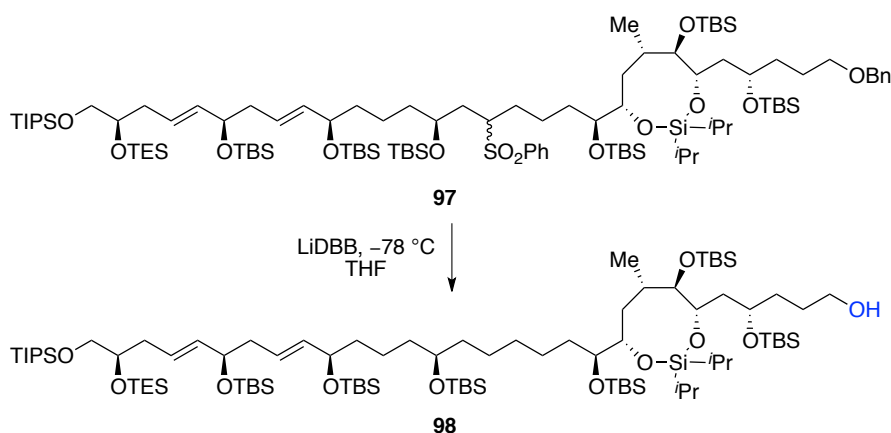
^1H NMR (500 MHz, CDCl_3) δ 7.87-7.85 (m, 2H), 7.65-7.61 (m, 1H), 7.56-7.52 (m, 2H), 7.34-7.33 (m, 4H), 7.30-7.26 (m, 1H), 5.63 (dt, $J = 15.0, 7.4$ Hz, 1H), 5.55 (dd, $J = 15.3, 7.7$ Hz, 1H), 5.48 (ddd, $J = 15.5, 6.3, 2.4$ Hz, 1H), 5.40 (dd, $J = 12.9, 6.6$ Hz, 1H), 4.52 (d, A of AB, $J_{AB} = 12.5$ Hz, 1H), 4.49 (d, B of AB, $J_{AB} = 12.4$ Hz, 1H), 4.08 (app. dt, $J = 9.5, 5.8$ Hz, 1H), 4.03-3.96 (m, 2H), 3.91-3.86 (m, 2H), 3.83-3.79 (m, 1H), 3.75-3.68 (m, 2H), 3.59 (dd, A of ABX, $J_{AB} = 9.7$ Hz, $J_{AX} = 5.3$ Hz, 1H), 3.50-3.46 (m, 3H), 3.49 (dd, B of ABX, $J_{AB} = 9.6$ Hz, $J_{BX} = 6.9$ Hz, 1H), 3.16-3.09 (m, 1H), 2.35 (app. dt, A of ABX₂, $J_{AB} = 13.2$ Hz, $J_{AX} = 6.4$ Hz, 1H), 2.27-2.13 (m, 2H), 1.94-1.53 (m, 11H), 1.46-1.27 (m, 13H), 1.10-0.99 (m, 17H), 1.06 (s, 12H), 1.05 (s, 6H), 0.95 (t, $J = 8.0$ Hz, 9H), 0.91-0.85 (m, 15H), 0.89 (s, 21H), 0.87 (s, 12H), 0.85 (s, 6H), 0.81 (s, 3H), 0.60 (q, $J = 7.9$ Hz, 6H), 0.07 (s, 3H), 0.06 (d, $J = 7.1$ Hz, 3H), 0.06 (s, 3H), 0.06 (d, $J = 7.2$ Hz, 3H), 0.04 (s, 9H), 0.03 (d, $J = 4.9$ Hz, 3H), 0.02 (s, 3H), 0.02 (d, $J = 6.3$ Hz, 3H), 0.01 (d, $J = 6.5$ Hz, 3H), -0.01 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 138.87 (e), 138.47 (e), 138.24 (e), 135.73 (o), 135.59 (o), 133.61 (o), 133.54 (o), 129.23 (o), 129.19 (o), 129.14 (o), 128.87 (o), 128.44 (o), 127.65 (o), 127.56 (o), 126.57 (o), 126.34 (o), 77.47 (o), 75.50 (o), 75.27 (o), 74.79 (o), 74.72 (o), 73.68 (o), 73.62 (o), 73.05 (o), 72.80 (e), 71.41 (o), 71.36 (o), 70.96 (e), 70.36 (o), 69.59 (o), 69.57 (o), 69.52 (o), 67.04 (e), 61.70 (o), 61.44 (o), 43.29 (e), 43.22 (e), 41.91 (e), 38.99 (e), 38.95 (e), 38.40 (e), 37.74 (e), 37.41 (e), 36.35 (e), 35.88 (e), 35.56 (e), 34.26 (o), 34.18 (o), 33.24 (e), 31.29 (e), 31.18 (e), 30.65 (e), 29.85 (e), 29.01 (e), 26.13 (o), 26.12 (o), 26.11 (o), 26.09 (o), 26.03 (o), 25.98 (o), 24.84 (e), 24.80 (e), 23.74 (e), 23.65 (e), 20.83 (e), 20.40 (e), 18.38 (e), 18.23 (e), 18.17 (o), 18.07 (e), 17.90 (o), 17.87 (o), 17.83 (o), 17.56 (o), 17.54 (o), 17.46

(o), 17.43 (o), 16.16 (o), 16.13 (o), 13.63 (o), 13.25 (o), 12.08 (o), 7.06 (o), 5.11 (e),
 -3.74 (o), -3.76 (o), -3.84 (o), -3.85 (o), -3.92 (o), -3.94 (o), -4.00 (o),
 -4.03 (o), -4.15 (o), -4.23 (o), -4.24 (o), -4.28 (o), -4.30 (o), -4.34 (o), -4.54 (o),
 -4.58 (o).

IR (Neat) 2952 (m), 2829 (m), 2857 (m), 1472 (w), 1463 (w), 1084 (m) cm^{-1} .

MS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{101}\text{H}_{200}\text{O}_{13}\text{NaSSi}_9$ 1928.3, found 1928.3



(*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-5-((4*S*,5*R*,6*S*,8*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2,2-diisopropyl-6-methyl-8-((5*S*,11*R*,15*R*,16*E*,19*R*,20*E*,23*R*)-11,15,19-tris((*tert*-butyldimethylsilyl)oxy)-26,26-diisopropyl-2,2,3,3,27-pentamethyl-23-((triethylsilyl)oxy)-4,25-dioxo-3,26-disilaoctacos-16,20-dien-5-yl)-1,3,2-dioxasilocan-4-yl)pentan-1-ol (98)

To a cooled to $-78\text{ }^{\circ}\text{C}$ solution of **97** (0.0463 g, 0.024 mmol) in THF (0.2 mL) was added LiDBB (0.6 mL, 0.3 M in THF, 0.180 mmol) dropwise until the mixture became deep green-blue and did not faint (TLC control). The reaction mixture was quenched with saturated aqueous NH_4Cl and partitioned between water and DCM. Phases were separated and aqueous was washed with DCM (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /hexanes – 1:20, 1:10, 1:7) afforded alcohol

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98 (0.026 g, 0.016 mmol, 64% yield) as a colourless oil.

$R_f = 0.21$ (Et₂O/hexanes – 1:7).

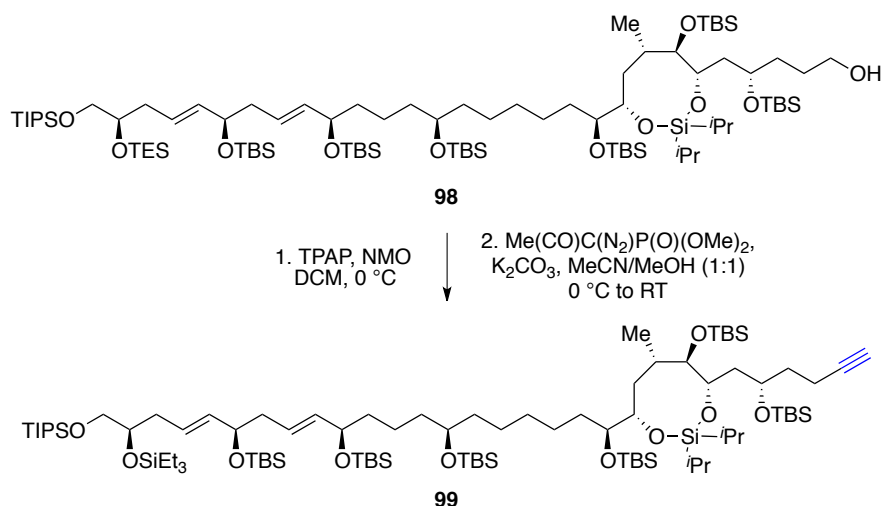
$[\alpha]_D^{20} +3.6$ (c 0.07, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 5.67 (dt, $J = 14.9, 7.4$ Hz, 1H), 5.53 (dt, $J = 14.8, 7.3$ Hz, 1H), 5.47 (dd, $J = 15.4, 6.9$ Hz, 1H), 5.42 (dd, $J = 15.2, 6.7$ Hz, 1H), 4.10-4.05 (m, 2H), 4.07 (q, $J = 5.6$ Hz, 1H), 4.01 (app. dt, $J = 10.0, 5.0$ Hz, 1H), 3.92 (dd, $J = 6.3, 4.4$ Hz, 1H), 3.91 (dd, $J = 4.4, 2.6$ Hz, 1H), 3.81 (app. dt, $J = 7.4, 4.7$ Hz, 1H), 3.71 (quintet, $J = 5.6$ Hz, 1H), 3.67-3.55 (m, 3H), 3.58 (dd, A of ABX, $J_{AB} = 9.7$ Hz, $J_{AX} = 5.4$ Hz, 1H), 3.49 (dd, B of ABX, $J_{AB} = 9.6$ Hz, $J_{BX} = 6.9$ Hz, 1H), 2.34 (app. dt, A of ABX₂, $J_{AB} = 13.2$ Hz, $J_{AX} = 6.4$ Hz, 1H), 2.24-2.13 (m, 4H), 1.95-1.87 (m, 2H), 1.83 (app. dt, A of ABX₂, $J_{AB} = 13.9$ Hz, $J_{AX} = 6.9$ Hz, 1H), 1.72 (ddd B of ABXY, $J_{AB} = 13.7$ Hz, $J_{BX} = 8.8$ Hz, $J_{BY} = 4.9$ Hz, 1H), 1.67-1.58 (m, 5H), 1.53 (q, $J = 6.2$ Hz, 1H), 1.49-1.20 (m, 15H), 1.12-1.01 (m, 35H), 0.95 (t, $J = 8.0$ Hz, 9H), 0.92-0.87 (m, 57H), 0.60 (q, $J = 7.9$ Hz, 6H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 6H), 0.04 (s, 3H), 0.04-0.03 (m, 15H), 0.02 (s, 3H), 0.01 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 135.98 (o), 135.61 (o), 126.32 (o), 126.28 (o), 77.42 (o), 75.79 (o), 75.09 (o), 73.79 (o), 73.65 (o), 73.07 (o), 72.48 (o), 71.62 (o), 69.57 (o), 67.05 (e), 63.47 (e), 42.33 (e), 41.89 (e), 38.92 (e), 37.43 (e), 37.41 (e), 37.29 (e), 36.51 (e), 34.37 (o), 33.01 (e), 31.00 (e), 30.41 (e), 27.70 (e), 26.57 (e), 26.13 (o), 26.11 (o), 26.09 (o), 26.08 (o), 26.04 (o), 25.52 (e), 21.46 (e), 18.38 (e), 18.30 (e), 18.28 (e), 18.24 (e), 18.17 (o), 17.84 (o), 17.49 (o), 17.42 (o), 16.19 (o), 13.67 (o), 13.35 (o), 12.09 (o), 7.06 (o), 5.11 (e), -3.66 (o), -3.95 (o), -4.06 (o), -4.23 (o), -4.30 (o), -4.31 (o), -4.35 (o), -4.59 (o).

IR (Neat) 3347 (br), 2929 (m), 2868 (m), 1472 (w), 1463 (w), 1067 (m) cm⁻¹.

MS (ESI, [M+Na]⁺) calcd for C₈₈H₁₉₀O₁₁NaSi₉ 1698.2, found 1698.3.



(4*S*,5*R*,6*S*,8*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)hex-5-yn-1-yl)-2,2-diisopropyl-6-methyl-8-((5*S*,11*R*,15*R*,16*E*,19*R*,20*E*,23*R*)-11,15,19-tris((*tert*-butyldimethylsilyl)oxy)-26,26-diisopropyl-2,2,3,3,27-pentamethyl-23-((triethylsilyl)oxy)-4,25-dioxo-3,26-disilaooctacosa-16,20-dien-5-yl)-1,3,2-dioxasilocane (99)

To a solution of alcohol **98** (0.0164 g, 9.78 μ mol) in DCM (0.1 mL) was added NMO (0.011 g, 0.098 mmol) and TPAP (0.9 mg, 2.56 μ mol) at 0 °C. After *ca.* 1 h (TLC control) the reaction mixture was passed through a pad of silica gel (washed with Et₂O/petroleum ether – 1:10) and concentrated to furnish crude aldehyde which was used in the following step without purification.

A solution of crude aldehyde in 1:1 mixture of MeOH and THF (0.2 mL) was treated with dimethyl 1-diazo-2-oxopropylphosphonate (0.019 g, 0.098 mmol) and K₂CO₃ (0.014 g, 0.098 mmol) at 0 °C. The reaction left to warm up to room temperature and stirred overnight. After *ca.* 16 h (TLC control) the reaction mixture was passed through a pad of silica gel (washed with Et₂O), concentrated and purified by flash chromatography (silica gel, Et₂O/hexanes – 1:100) to afford alkyne **99** (0.0145 g, 8.68 μ mol, 89 % yield over 2 steps) as a colourless oil.

R_f = 0.89 (Et₂O/hexanes – 1:1).

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$[\alpha]_{\text{D}}^{20} -3.2$ (c 0.32, CHCl_3).

^1H NMR (500 MHz, CDCl_3) δ 5.65 (dt, $J = 15.0, 7.4$ Hz, 1H), 5.53 (dt, $J = 14.9, 7.3$ Hz, 1H), 5.47 (dd, $J = 15.5, 6.3$ Hz, 1H), 5.41 (dd, $J = 15.3, 6.7$ Hz, 1H), 4.06 (q, $J = 6.3$ Hz, 1H), 4.04-3.99 (m, 2H), 3.92-3.89 (m, 2H), 3.78 (app. dt, $J = 8.0, 4.1$ Hz, 1H), 3.70 (quintet, $J = 5.7$ Hz, 1H), 3.61-3.54 (m, 2H), 3.58 (dd, A of ABX, $J_{AB} = 9.5$ Hz, $J_{AX} = 5.3$ Hz, 1H), 3.48 (dd, B of ABX, $J_{AB} = 9.6$ Hz, $J_{BX} = 6.9$ Hz, 1H), 2.34 (app. dt, A of ABX₂, $J_{AB} = 13.0$ Hz, $J_{AX} = 6.2$ Hz, 1H), 2.29 (dd, A of ABX, $J_{AB} = 11.2$ Hz, $J_{AX} = 3.0$ Hz, 1H), 2.28-2.25 (m, 1H), 2.21 (quintet, $J = 7.0$ Hz, 1H), 2.17-2.13 (m, 2H), 1.93 (t, $J = 2.6$ Hz, 1H), 1.89 (dd, B of ABX, $J_{AB} = 10.7$ Hz, $J_{BX} = 6.2$ Hz, 1H), 1.82 (app. dt, A of ABX₂, $J_{AB} = 13.5$ Hz, $J_{AX} = 6.9$ Hz, 1H), 1.78 (dd, B of ABX, $J_{AB} = 8.8$ Hz, $J_{BX} = 3.3$ Hz, 1H), 1.68-1.51 (m, 2H), 1.66 (ddd B of ABXY, $J_{AB} = 14.0$ Hz, $J_{BX} = 8.2$ Hz, $J_{BY} = 4.1$ Hz, 1H), 1.53 (d, B of ABX, $J_{AB} = 13.7$ Hz, $J_{BX} = 7.7$ Hz, 1H), 1.47-1.38 (m, 6H), 1.34-1.18 (m, 10H), 1.10-0.98 (m, 35H), 0.95 (t, $J = 7.9$ Hz, 9H), 0.90-0.87 (m, 57H), 0.59 (q, $J = 7.9$ Hz, 6H), 0.08 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (m, 3H), 0.03 (s, 6H), 0.02 (s, 6H), 0.01 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 135.94 (o), 135.58 (o), 126.19 (o), 126.14 (o), 85.08 (e), 77.33 (o), 75.70 (o), 75.07 (o), 73.77 (o), 73.63 (o), 73.02 (o), 72.45 (o), 71.44 (o), 68.47 (o), 68.33 (e), 67.00 (e), 42.96 (e), 41.87 (e), 38.89 (e), 37.39 (e), 37.26 (e), 36.33 (e), 35.60 (e), 34.45 (o), 30.85 (e), 30.38 (e), 26.57 (e), 26.15 (o), 26.09 (o), 26.08 (o), 26.05 (o), 26.02 (o), 25.51 (e), 21.47 (e), 19.93 (e), 18.38 (e), 18.29 (e), 18.22 (e), 18.16 (o), 17.81 (o), 17.50 (o), 17.41 (o), 16.08 (o), 13.87 (e), 13.63 (o), 13.31 (o), 12.04 (o), 7.07 (o), 5.07 (e), -3.65 (o), -3.84 (o), -3.94 (o), -3.96 (o), -4.07 (o), -4.25 (o), -4.33 (o), -4.45 (o), -4.60 (o).

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IR (Neat) 3315 (w), 2952 (m), 2929 (m), 2858 (m), 1463 (w), 1252 (w), 1071 (m) cm^{-1} .

MS (ESI, $[\text{M}+\text{Na}+\text{H}]^+$) calcd for $\text{C}_{89}\text{H}_{189}\text{O}_{10}\text{NaSi}_9$ 1693.2, found 1693.2.

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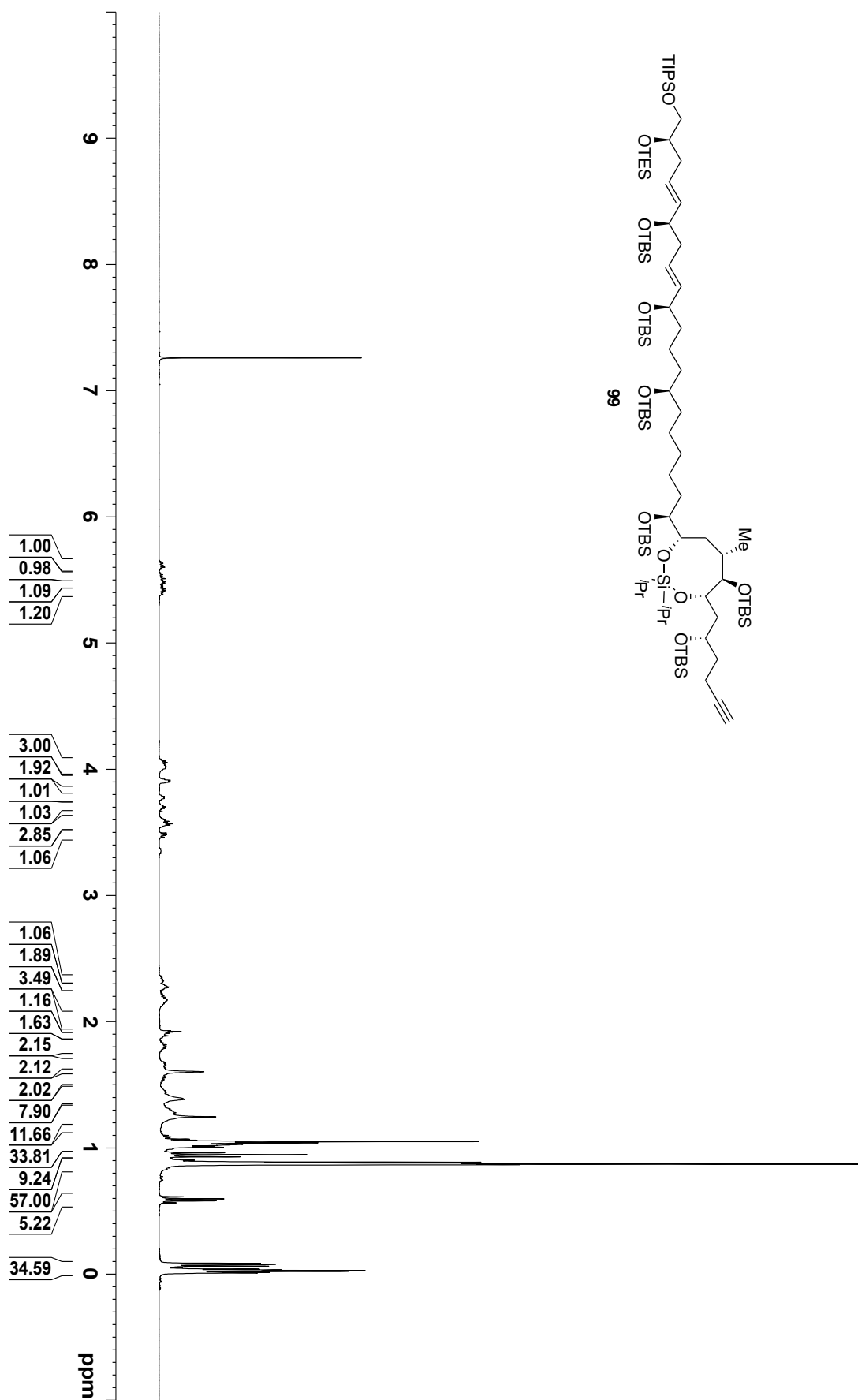
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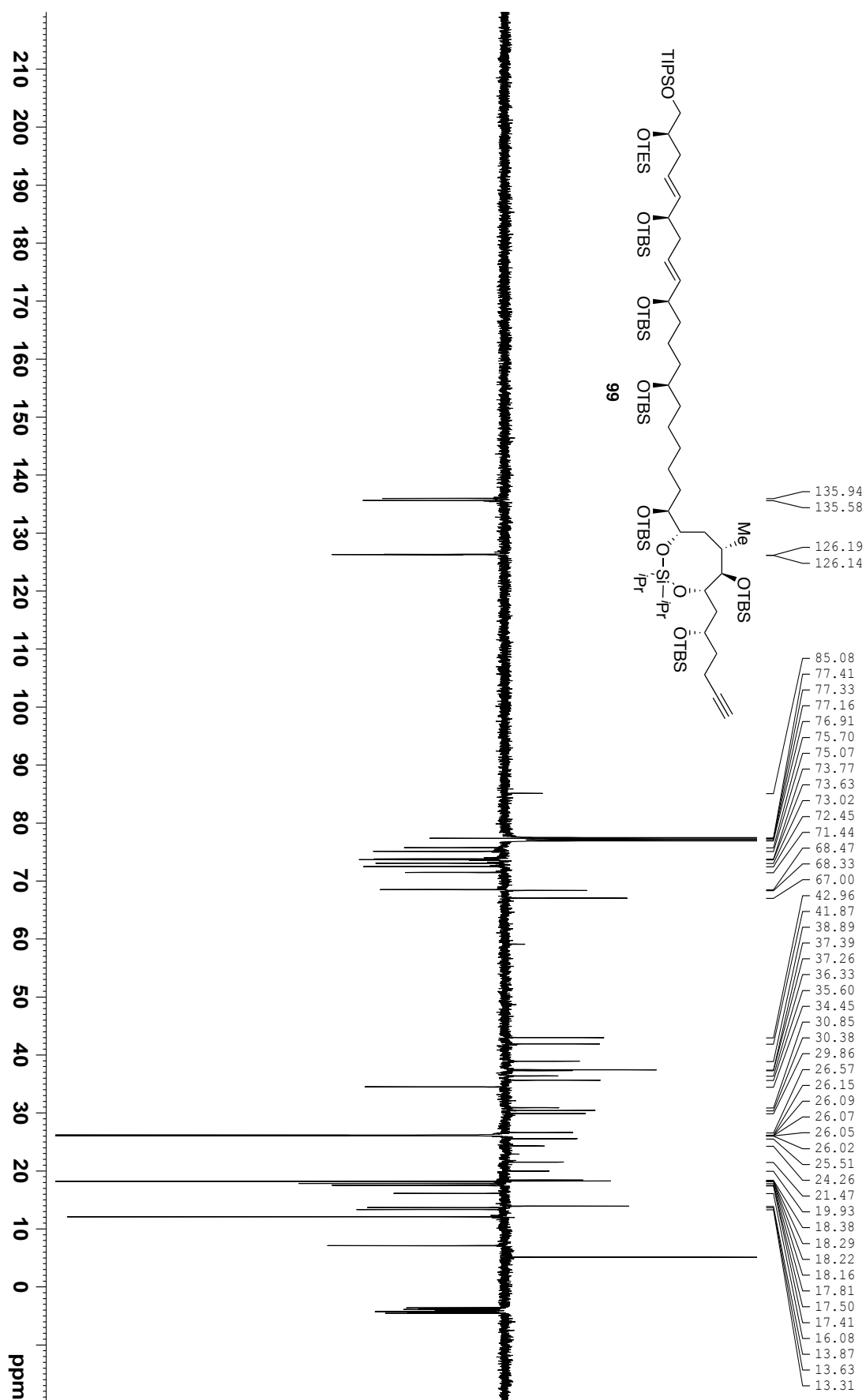
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4.20 Appendix B. ^1H and APT Spectrums for Compound 99



Chapter 5

Synthetic Studies of the *bis*-THP Fragment of Amphidinol 3

5.1 Introduction to Tetrahydropyran Segment of Amphidinol 3

Synthetically, the *bis*-tetrahydropyran (*bis*-THP) fragment of amphidinol 3 is considered to be the most challenging in the molecule (Figure 5.1.1). This C31-C52 subunit comprises a polyol chain having two highly functionalised pentasubstituted tetrahydropyran rings isolated by three carbon spacer and accounts for 15 of the 24 stereogenic centres found in the molecule.

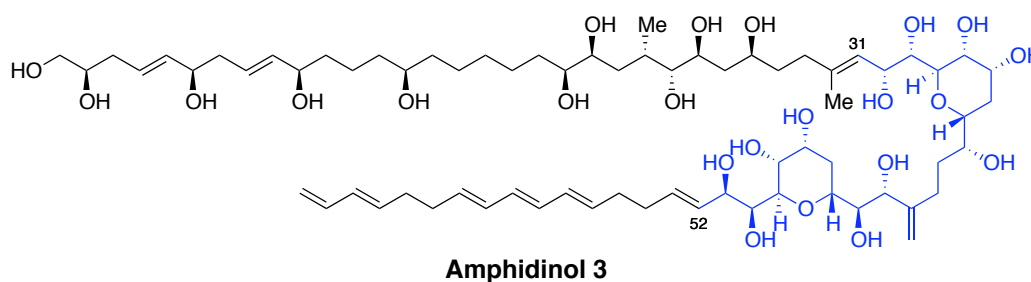
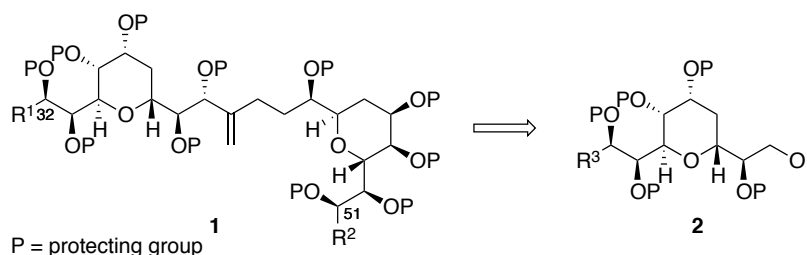


Figure 5.1.1: *Bis-Tetrahydropyran Fragment in Amphidinol 3*

A crucial feature of this section of the molecule is the presence of two identical tetrahydropyran rings. This fact allows the synthetic plan to be simplified, thereby providing a more convergent synthesis. As highlighted in Scheme 5.1.1, the C32-C52 fragment could be constructed *via* the preparation of the common intermediate **2**, which bears most of the required stereocentres.

Scheme 5.1.1: *Strategic Disconnection in the Retrosynthetic Analysis of the bis-THP fragment of AM3*

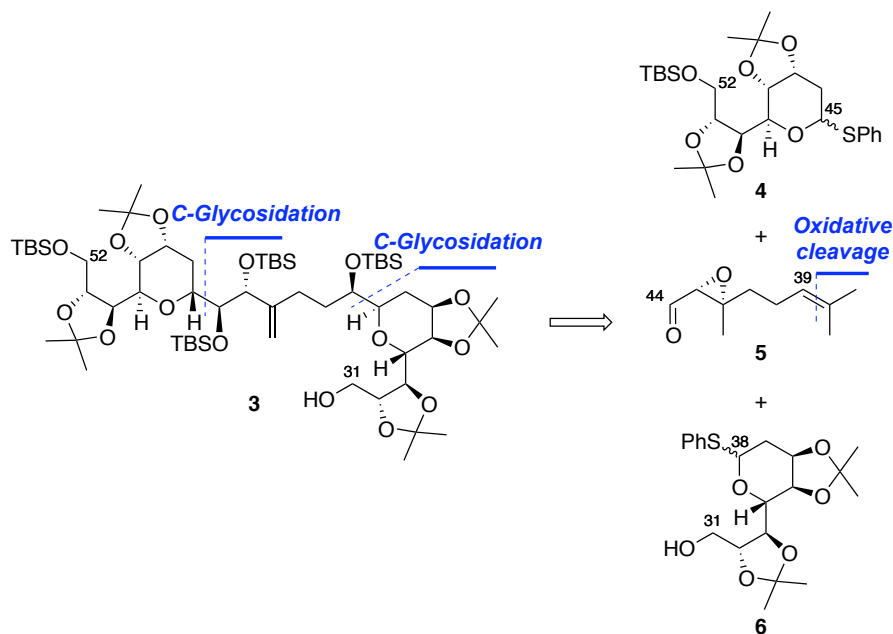


The aim of this chapter is to overview all published synthetic efforts toward AM3 in the context of the formation of the *bis*-THP segment, to highlight the strategies developed to exploit the partial symmetry of the natural product and review reported synthesis of fragment **2**.

5.2 Rychnovsky's Synthesis of the C31-C67 Fragment of Amphidinol 3

In 2005, the Rychnovsky group was the first to publish an approach towards the common tetrahydropyran fragment in 2005.¹ Their initial advent to the *bis*-THP fragment **3** was based on the synthesis of a common 2-thiophenyl tetrahydropyran intermediate **4** followed by successive C-glycosidation of its lithium anion nucleophile at C45 with the known epoxyaldehyde **5** (Scheme 5.2.1).

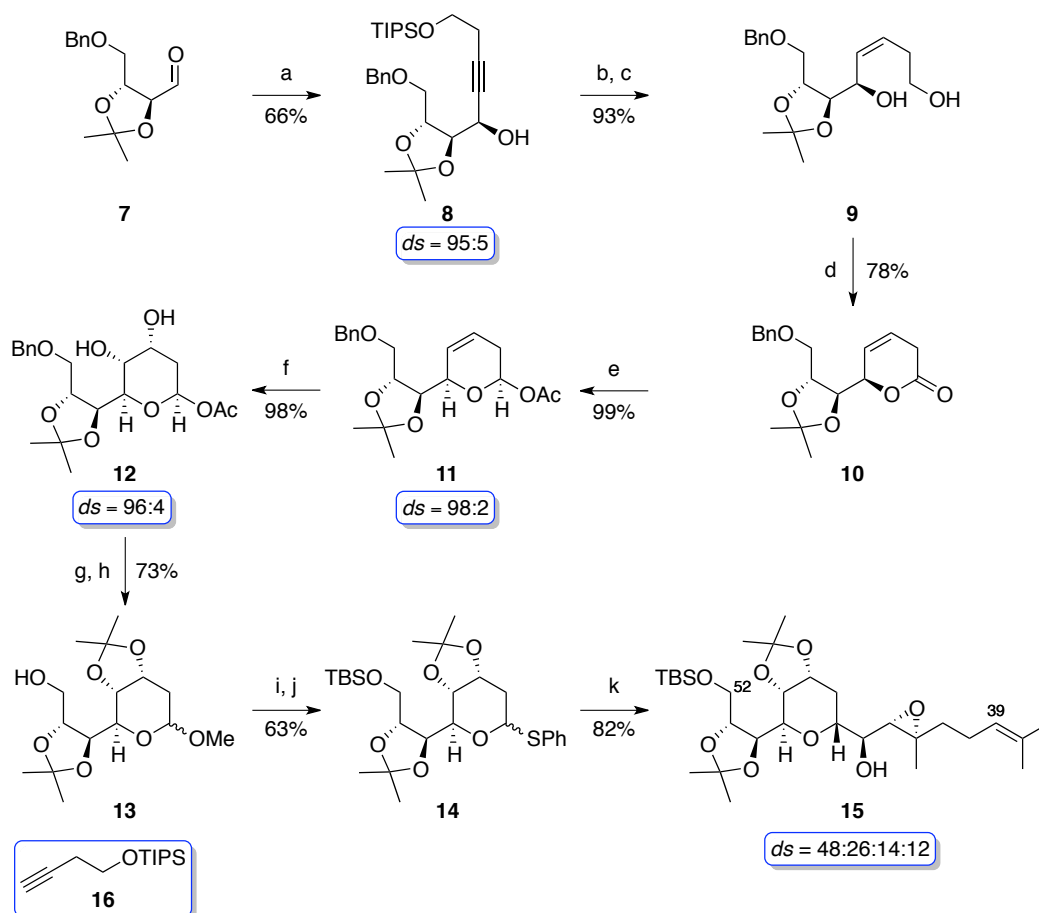
Scheme 5.2.1: Rychnovsky's Retrosynthetic Analysis of the *bis*-THP Fragment of Amphidinol 3



The synthetic sequence leading to **15** is shown in Scheme 5.2.2. Titanium acetylide addition to known aldehyde **7**² (available in 5 steps from *D*-(-)-tartaric acid) furnished alcohol **8** with excellent diastereocontrol (*ds* = 95:5). Selective

alkyne reduction to the corresponding (*Z*)-olefin was effected with P-2 nickel,³ followed by desilylation with TBAF. Successive chemoselective TEMPO oxidation of primary alcohol **9** afforded the δ -lactone **10** in good yield.⁴

Scheme 5.2.2: Synthesis of the C39-C52 Fragment of Amphidinol 3



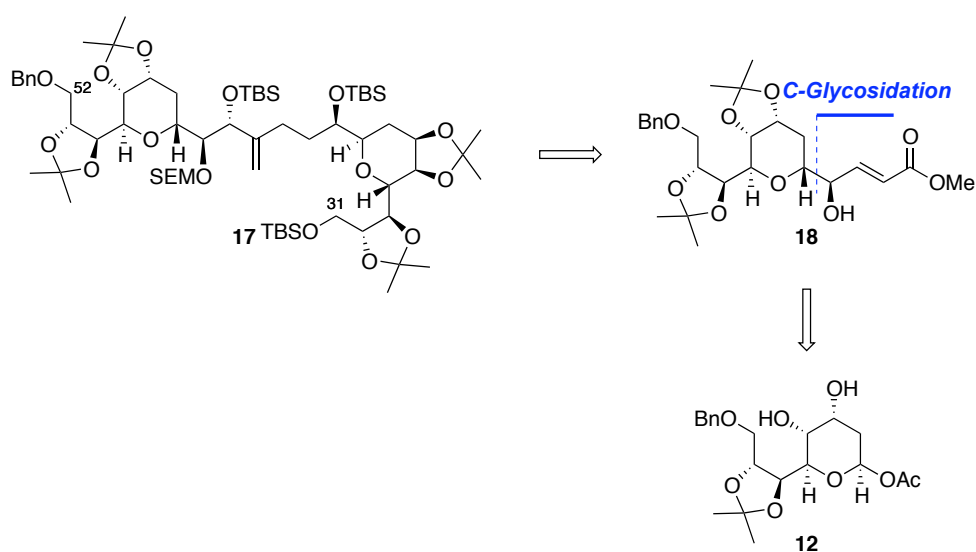
Reaction conditions: a) i. **16**, ⁿBuLi, THF, -78 °C. ii. TiCl₄, Ti(OⁱPr)₄, then **1**, THF, -78 °C to RT, *ds* = 95:5, 66%. b) H₂, Ni(OAc)₂·4H₂O, NaBH₄, NH₂(CH₂)₂NH₂, EtOH, RT, 98%. c) TBAF, THF, RT, 95%. d) *cat.* TEMPO, *cat.* TBACl, NCS, DCM/pH 8.6 buff. (1.3:1), RT, 78%. e) DIBAL-H, DCM, -78 °C, then Ac₂O, Py, DMAP, DCM, -78 °C to RT, *ds* = 98:2, 99%. f) *cat.* OsO₄, NMO, acetone/H₂O (8:1), RT, *ds* = 96:4, 98%. g) 2,2-DMP, *cat.* TsOH, benzene, RT, 74%. h) H₂, *cat.* Pd/C, MeOH, RT, 98%. i) TBSCl, imidazole, DMF, RT, 90%. j) PhSTMS, ZnI₂, TBAI, DCE, 85 °C, 70%. k) LiDBB, THF, -78 °C, then **5**, *ds* = 48:26:14:12, 82%.

Anomeric acetate **11** formation from lactone **10** was achieved in excellent yield and with high diastereoselectivity (*ds* = 98:2) *via* DIBAL-H reduction and acetylation of intermediate lactol.⁵ Upjohn dihydroxylation⁶ proceeded from less sterically encumbered face of the alkene **11** and produced diol **12** with excellent

diastereocontrol ($ds = 96:4$). It is noteworthy that dihydroxylation of lactone **10** was shown to be less selective, delivering a 4:1 mixture of 1,2-*cis* diols. Acetonide formation of **12** and hydrogenolysis of the primary benzyl ether in methanol afforded alcohol **13** as an inconsequential 1:1 mixture of *O*-methyl anomers and set the stage for the formation of the *C*-glycoside donor **14**. Thus, TBS protection of primary alcohol **13**, followed by ZnI_2 mediated PhSTMS addition gave phenylthio acetal **14**, which is the common THP fragment. Subsequent reductive lithiation of the latter with LiDBB^7 at $-78\text{ }^\circ\text{C}$ and addition of epoxy aldehyde **5**⁸ resulted in formation of alcohol **15** with poor diastereocontrol ($ds = 48:26:14:12$), albeit slightly favouring the desired isomer. The modest stereocontrol in the key coupling reaction was attributed to non-selective axial radical formation during the lithiation step.

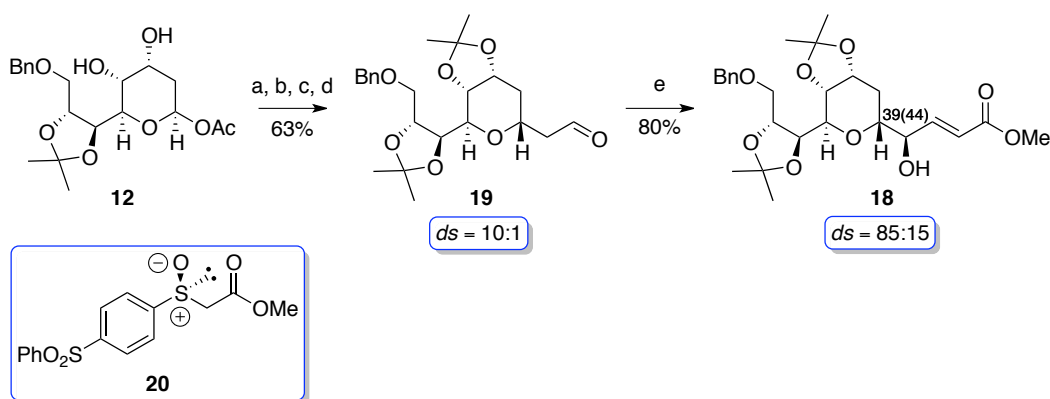
The futile *C*-glycosidation led to a reinvestigation of the synthetic plan.⁹ The alternative route, presented in Scheme 5.2.3, maintained a similar coupling strategy. However, the common THP fragment selected in this case was the α,β -unsaturated ester **18**, which in turn can be accessed from earlier described diol **12** (*vide supra*).

Scheme 5.2.3: Revised Retrosynthetic Analysis of the bis-THP Fragment of *Amphidinol 3*



The new route to the common fragment **18** is shown in Scheme 5.2.4. Axial addition of allylTMS¹⁰ furnished the required 2,6-*trans*-THP ring with excellent stereocontrol (*ds* = 10:1). Subsequent protection of diol, followed by ozonolysis provided aldehyde **19**. Knoevenagel condensation with the chiral sulfoxide **21**¹¹ using conditions developed by Trost and Malart¹² established final stereogenic centre at C39(C44) of **18** in acceptable yield and selectivity (*ds* = 85:15).

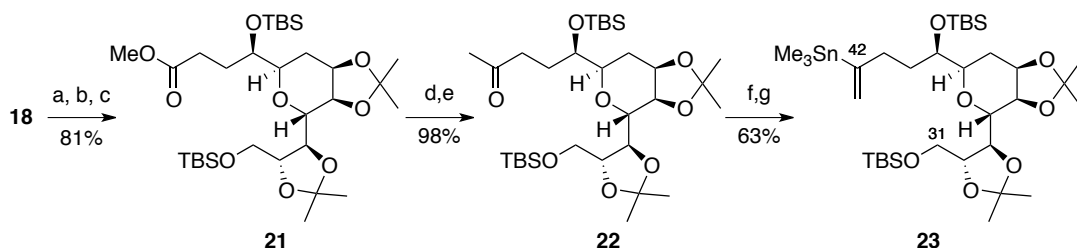
Scheme 5.2.4: Revised Synthesis of the Common THP Fragment



Reaction conditions: a) AllylTMS, TMSOTf, DTBMP, DCM, $-78\text{ }^{\circ}\text{C}$, *ds* = 10:1. b) K_2CO_3 , MeOH, RT, 82% over two steps. c) 2,2-DMP, *cat.* TsOH, C_6H_6 , RT, 82%. d) O_3 , sudan III, DCM, then PPh_3 , $-78\text{ }^{\circ}\text{C}$ to RT, 94%. e) **20**, piperidine, MeCN, $-5\text{ }^{\circ}\text{C}$, *ds* = 85:15, 80%.

Further elaboration of **18** to stannane **23** began with TBS protection, followed by strategic protecting group exchange *via* hydrogenative debenzoylation, with concomitant olefin reduction, and primary alcohol silylation (Scheme 5.2.5).

Scheme 5.2.5: Synthesis of the C31-C42 THP Fragment

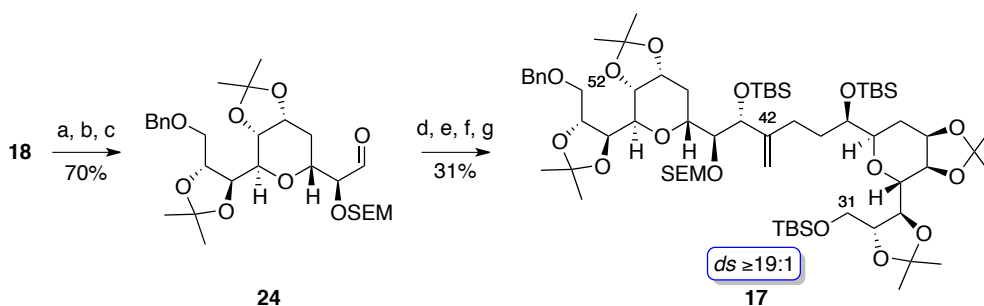


Reaction conditions: a) TBSOTf, 2,6-lutidine, DCM, $0\text{ }^{\circ}\text{C}$ to RT, 97%. b) H_2 (90 psi), Pd/C, RT, THF. c) TBSOTf, 2,6-lutidine, DCM, $0\text{ }^{\circ}\text{C}$ to RT, (84% over two steps). d) $\text{Me}(\text{OMe})\text{NH}\cdot\text{HCl}$, $n\text{-BuLi}$, THF, $-78\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$, then **21**, THF, $-78\text{ }^{\circ}\text{C}$. e) MeMgBr , THF, $0\text{ }^{\circ}\text{C}$ (98% for two steps). f) LDA, THF, $-78\text{ }^{\circ}\text{C}$, then *N*-(5-chloro-2-pyridyl)triflimide, 74%. g) $\text{Me}_3\text{SnSnMe}_3$, LiCl, *cat.* $[\text{Pd}(\text{PPh}_3)_4]$, THF, $80\text{ }^{\circ}\text{C}$ in a sealed tube, 85%.

Ester **21** was transformed to ketone **22** with intermediate formation of a Weinreb amide.¹³ The construction of vinyl stannane **23** was secured through a reaction sequence involving kinetic deprotonation of **22**, formation of an enol triflate using Comins reagent¹⁴ and Stille cross-coupling with hexamethylditin¹⁵ (63% for 2 steps).

With the C31-C42 fragment in hand, efforts towards the synthesis of the second THP fragment and assembly of full segment were effected (Scheme 5.2.6). SEM protection of alcohol **18**,¹⁶ followed by Johnson-Lemieux oxidative cleavage of the olefin afforded α -alkoxy aldehyde **24**.¹⁷ The union of the two THP fragments was achieved using lithium-tin exchange of **23**, followed by addition of aldehyde **24**. The resulting 1:1 mixture of diastereoisomers was oxidised with Dess-Martin periodinane¹⁸ and the resultant ketone was submitted to a chelation-controlled reduction with $\text{Zn}(\text{BH}_4)_2$, which provided the required alcohol as a single stereoisomer. Finally, silylation of the latter furnished the fully protected C31-C52 *bis*-THP fragment of amphidinol 3.

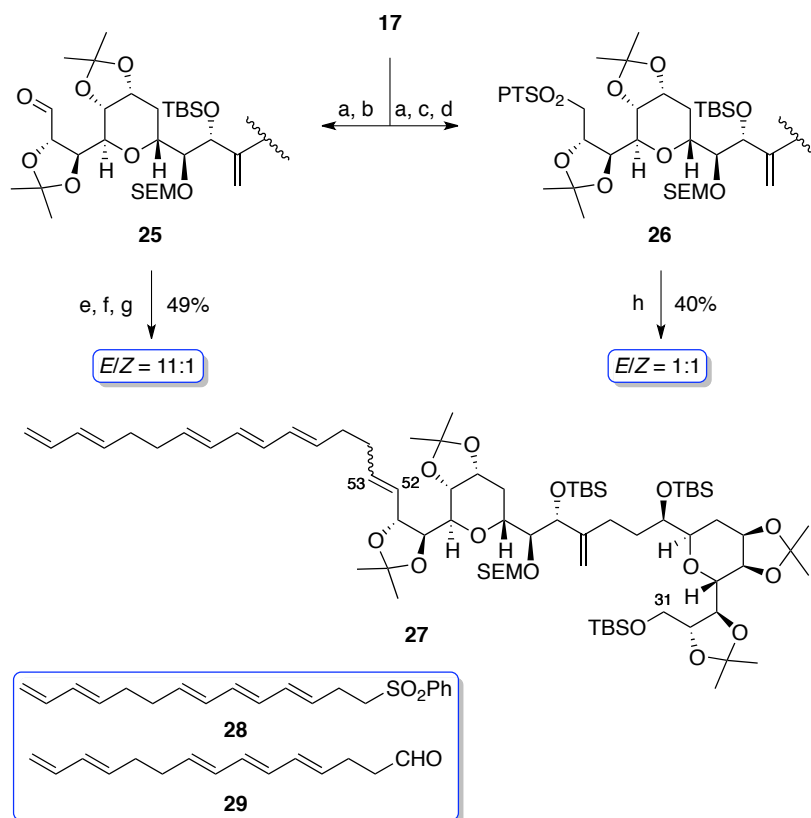
Scheme 5.2.6: *Synthesis of the C43-C52 THP Fragment and Elaboration of the bis-THP Segment 17*



Reaction conditions: a) SEMCl, DIPEA, DCM, 40 °C, 85%. b) *cat.* OsO_4 , NMO, acetone/ H_2O (8:1), RT. c) NaIO_4 , THF/ H_2O (1:1), RT, 82% over two steps. d) **23**, $n\text{BuLi}$, THF, -78°C , then **24**, *ds* = 1:1. e) DMP, Py, DCM, RT. f) $\text{Zn}(\text{BH}_4)_2$, Et_2O , -35°C , *ds* $\geq 19:1$, 43% over three steps. g) TBSOTf, 2,6-lutidine, DCM, RT, 73%.

Additional studies to install the polyene chain to the *bis*-THP fragment **17** using Julia-type coupling were explored (Scheme 5.2.7). Reductive debenzoylation of **17** with LiDBB⁷ afforded a primary alcohol, which was further oxidised to aldehyde **25** using Dess-Martin periodinane.¹⁸ Julia-Lythgoe coupling¹⁹ with the lithiated sulfone **28** furnished the β -hydroxy sulfone product in 76% yield. Successive acylation with benzoic anhydride and reductive elimination using sodium amalgam resulted in the C31-C67 fragment of AM3 with excellent 11:1 *E/Z* ratio.

Scheme 5.2.7: Polyene Linkup with the *bis*-THP Fragment



Reaction conditions: a) LiDBB, THF, $-78\text{ }^{\circ}\text{C}$, 98%. b) DMP, Py, DCM, $0\text{ }^{\circ}\text{C}$ to RT, 100%. c) PTSH, PPh_3 , DIAD, THF, $0\text{ }^{\circ}\text{C}$ to RT, 86%. d) $\text{Mo}_7\text{O}_{24}(\text{NH}_4)_6 \cdot 4\text{H}_2\text{O}$, H_2O_2 , EtOH, 59%. e) **28**, LDA, THF, $-78\text{ }^{\circ}\text{C}$, then **25**, THF, $-78\text{ }^{\circ}\text{C}$ to RT, 76%. f) Bz_2O , DMAP, Py, DCM, RT, 89%. g) Na(Hg), Na_2HPO_4 , THF/MeOH (3:1), $-20\text{ }^{\circ}\text{C}$, *E/Z* = 11:1, 72%. h) **26**, KHMDS, THF, $-78\text{ }^{\circ}\text{C}$, then **29**, THF, $-78\text{ }^{\circ}\text{C}$ to RT, *E/Z* = 1:1, 40%.

In sharp contrast, when Julia-Kocienski olefination²⁰ was applied to aldehyde **29** and sulfone **26** (obtained by debenzoylation of **17**, Mitsunobu reaction with

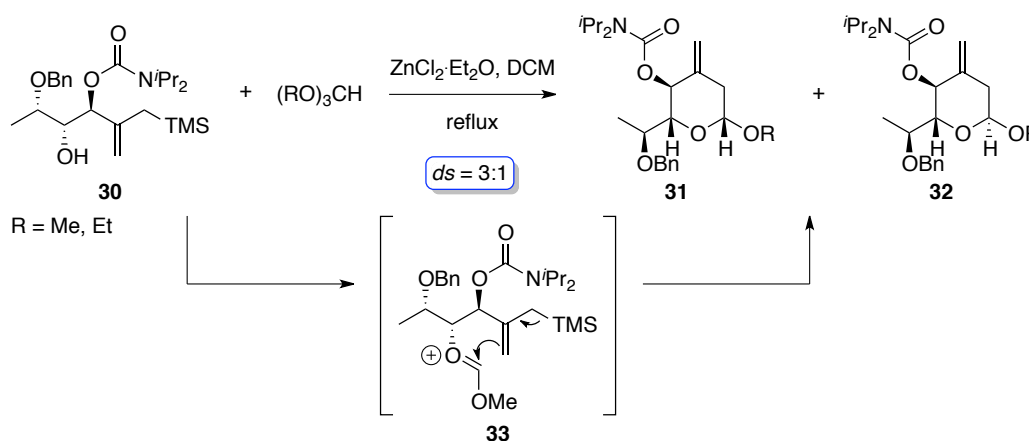
PTSH²¹ and molybdate-mediated oxidation),²² the coupling product **27** was obtained in 40% yield as a mixture of isomers (*E/Z* = 1:1).

In conclusion, Rychnovsky and co-workers developed a convergent route to the C31-C52 *bis*-THP segment of amphidinol 3, which constitutes of 22 longest linear steps with 3.7% yield (12 steps to the common THP fragment, 24% yield). The key assembly steps included *C*-glycosidation to produce the 2,6-*trans*-THP ring, which was followed by organolithium coupling with an aldehyde to assemble the *bis*-THP segment. Additionally, extensive studies were carried out for the incorporation of polyene moiety into the molecule; showing that Julia-Lythgoe olefination was the method of the choice to deliver superior *E/Z* selectivity and yield.

5.3 Marko's Synthesis of Polysubstituted 2,6-*anti*-Tetrahydropyrans

Marko and co-workers were next to disclose their account towards the synthesis of highly functionalised tetrahydropyrans found in AM3.²³ They have developed methodology that allowed preparation of 2,6-*anti*-configured tetrahydropyrans having required functionalities and the stereochemical relationships of amphidinol 3.

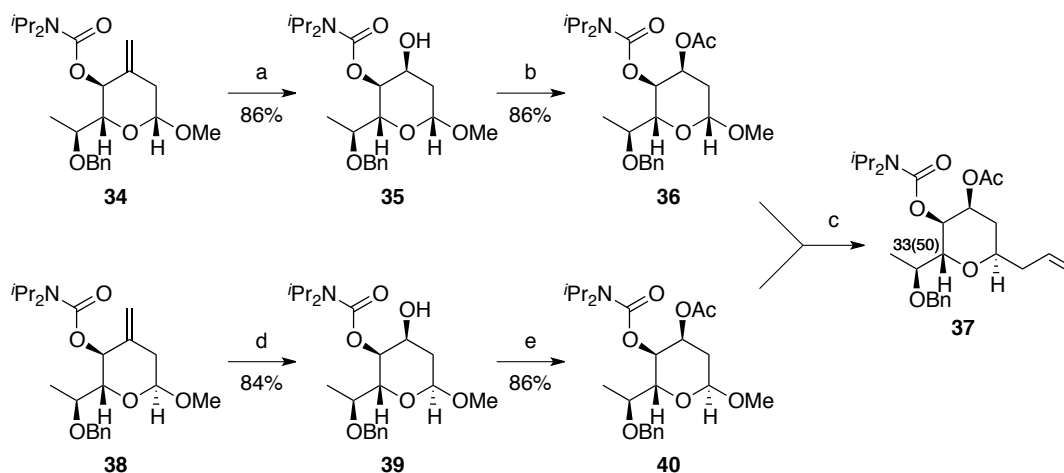
Scheme 5.3.1: Lewis Acid Mediated Synthesis of *syn*- and *anti*-Tetrahydropyrans



Thus, zinc(II) chloride mediated condensation of alcohol **30** with an alkyl orthoester produced a 3:1 mixture of pyrans **31/32** favouring the all *syn* isomer (Scheme 5.3.1). The reaction proceeds *via* an intermediate ion, which presumably undergoes an Intramolecular Silyl-Modified Sakurai (ISMS) reaction.²⁴

The authors envisaged the application of this methodology to the synthesis of the fully functionalised THP fragment of amphidinol 3 (Scheme 5.3.2). Each of the diastereomeric pyrans was used independently and the exocyclic double bonds in **34** and **38** were cleaved by ozonolysis in good yield. Stereoselective reduction of the ketone derived from **38** with various bulky reducing reagents proceeded smoothly to afford the equatorial alcohol. In contrast, reduction of the ketone obtained from **34** proceeded stereoselectively only with DIBAL-H. Both alcohols were acetylated and subjected to TMSOTf mediated axial allylation¹⁰ to provide *anti*-**37** in excellent yield.

Scheme 5.3.2: *Elaboration of the Highly Substituted anti-Tetrahydropyran 37*



Reaction conditions: a) O₃, Me₂S, DCM, -78 °C, then toluene, DIBAL-H, -40 °C, 86%. b) Ac₂O, Py, DMAP, RT, 86%. c) AllylTMS, TMSOTf, MeCN, -40 °C to 0 °C, 92%. d) O₃, Me₂S, DCM, -78 °C, then L-Selectride, THF, -78 °C, 84%. e) Ac₂O, Py, DMAP, RT, 86%.

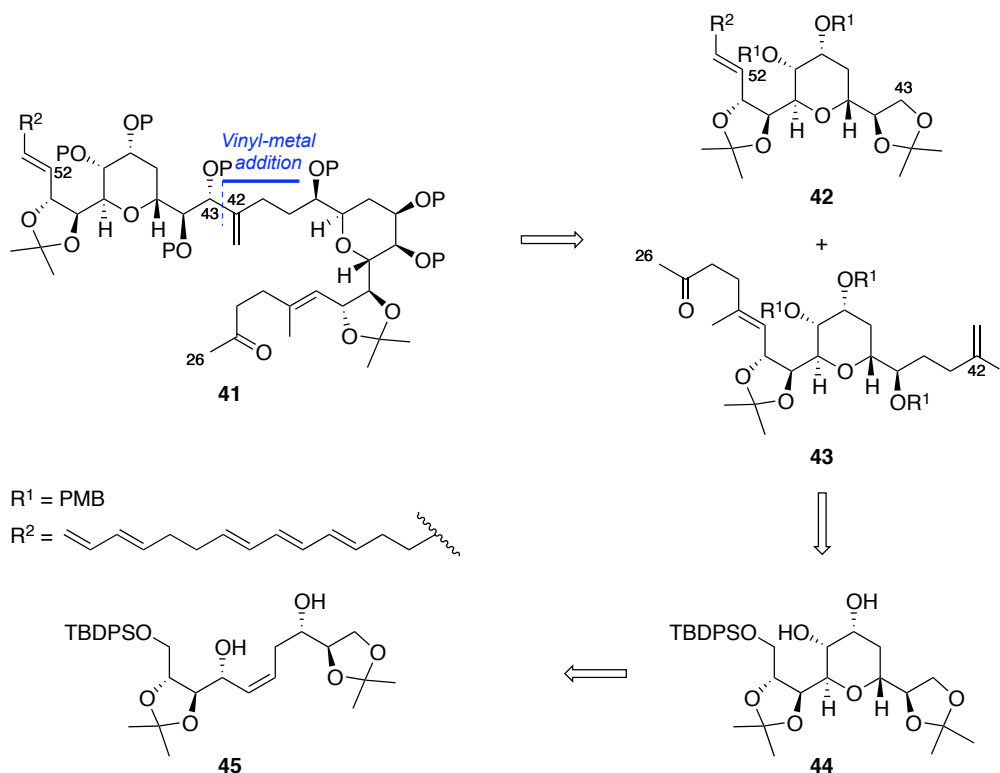
In summary, Marko and co-workers have developed an appealing methodology that provides the pseudoenantiomer of the common THP intermediate

found in amphidinol 3, epimeric at C33(50), in 8 longest linear steps and with 43% overall yield. Further elaboration of this method could in principle provide rapid access to the *bis*-THP segment of AM3.

5.4 Roush's Synthesis of C26-C42 and C43-C67 Fragments of Amphidinol 3

In 2005 Roush, Flamme and Hicks reported an account towards the synthesis of the C43-C67 fragment of amphidinol 3.²⁵ During the course of their studies, they applied previously developed double allylboration methodology²⁶ to access the THP rings present in the natural product.

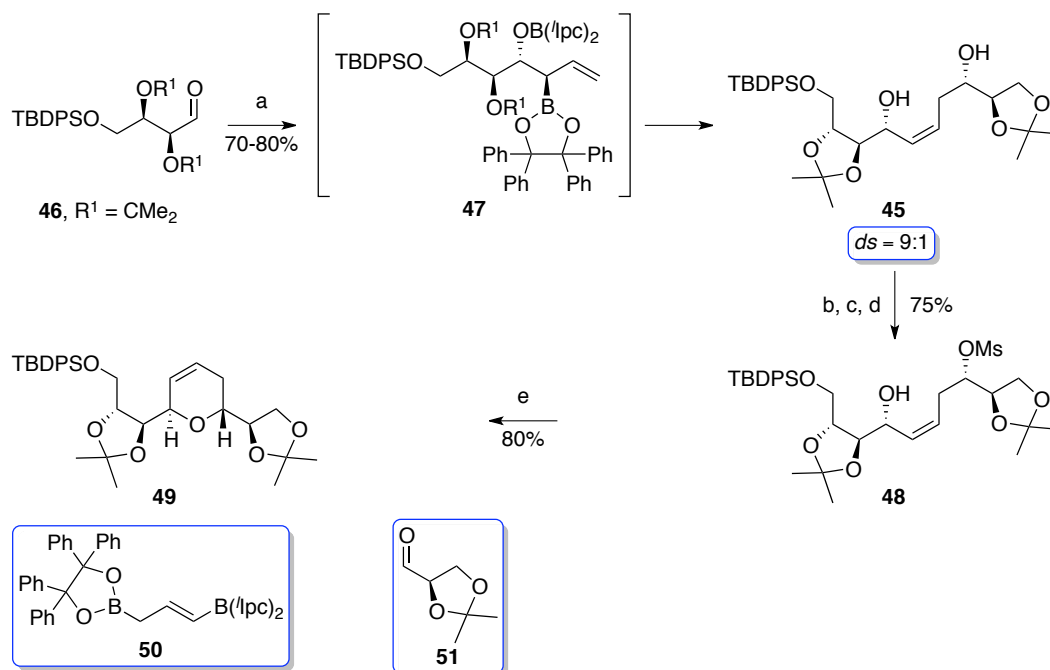
Scheme 5.4.1: Roush's Retrosynthetic Analysis of the *bis*-THP Fragment of AM3



The retrosynthetic analysis of **41** reveals a pivotal disconnection of the C43-C42 bond that gives tetrahydropyrans **42** and **43**, which are available from the common intermediate **44** (Scheme 5.4.1). The latter could be obtained from *syn*-1,5-diol **45** using a dehydrative cyclisation.²⁷

Initial studies were directed towards the preparation of the differentially protected cyclisation precursor **48** (Scheme 5.4.2). A double allylboration reaction between aldehydes **46**, **51** and *in situ* generated **50** (prepared by hydroboration of 2-allenyldioxaborolane with $^t\text{Ipc}_2\text{BH}$) afforded the 1,5-*syn* diol **45**, through the formation of intermediate **47**, in good yield and selectivity (*ds* = 9:1). Chemoselective mesylation of **48** met with no success, thus a stepwise approach was implemented.²⁷ Selective silylation of allylic alcohol was achieved at $-78\text{ }^\circ\text{C}$ with excellent regiocontrol (*rr* >20:1). Subsequent mesylation and TES ether removal afforded the desired cyclisation precursor **48** in 75% overall yield. After extensive optimisation of the cyclisation conditions, dihydropyran **49** was obtained upon treatment with KO^tBu in 80% yield with concomitant formation of a conjugated diene as an elimination by-product.

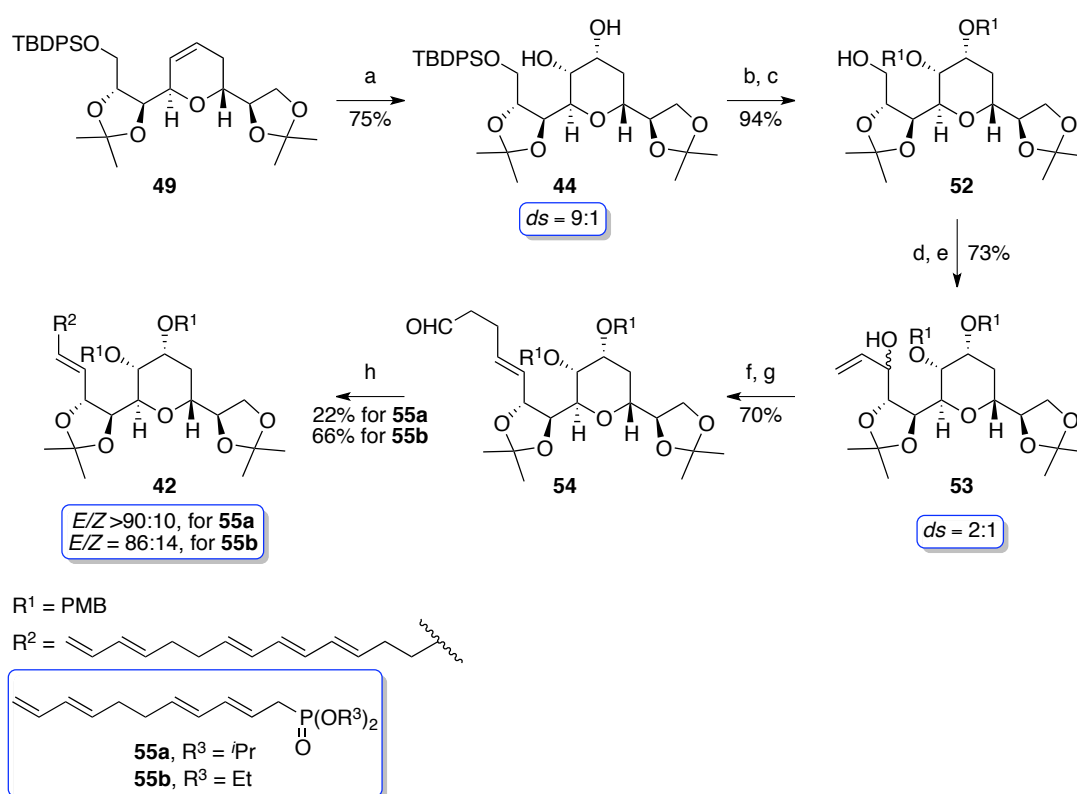
Scheme 5.4.2: Synthesis of the Cyclisation Precursor **48 via Double Allylboration**



Reaction conditions: a) **50**, DCM, $-78\text{ }^\circ\text{C}$, then **51**, DCM, $-78\text{ }^\circ\text{C}$ to RT, *ds* = 9:1, 70-80%. b) TESCl, imid, *cat.* DMAP, DCM/DMF (1:1), $-78\text{ }^\circ\text{C}$, 81%. c) MsCl, Et_3N , *cat.* DMAP, DCM, $0\text{ }^\circ\text{C}$. d) AcOH, $\text{H}_2\text{O}/\text{THF}$ (1:1), RT, 93% over 2 steps. e) KO^tBu , $^t\text{AmOH}$, $0\text{ }^\circ\text{C}$, (0.03 M), 80%.

With **49** in hand, stereoselective dihydroxylation using a stoichiometric amount of osmium oxidant produced the common THP fragment **44** in 75% yield and with good selectivity ($ds = 9:1$) (Scheme 5.4.3).²⁸ In contrast, when catalytic osmylation⁶ was implemented, the reaction afforded poor stereocontrol ($ds = 1.6:1$, 80% yield), whereas Sharpless conditions,²⁹ using the chiral DHQD-IND ligand,³⁰ gave 3:1 selectivity favouring the required isomer in excellent 97% yield. Diol protection as *bis*-PMB ether and primary TBDPS ether removal afforded alcohol **52**. Swern oxidation³¹ and vinyl Grignard addition furnished **53** as an inconsequential 2:1 mixture of diastereoisomers, which set stage for Johnson-Claisen ortho ester rearrangement.³²

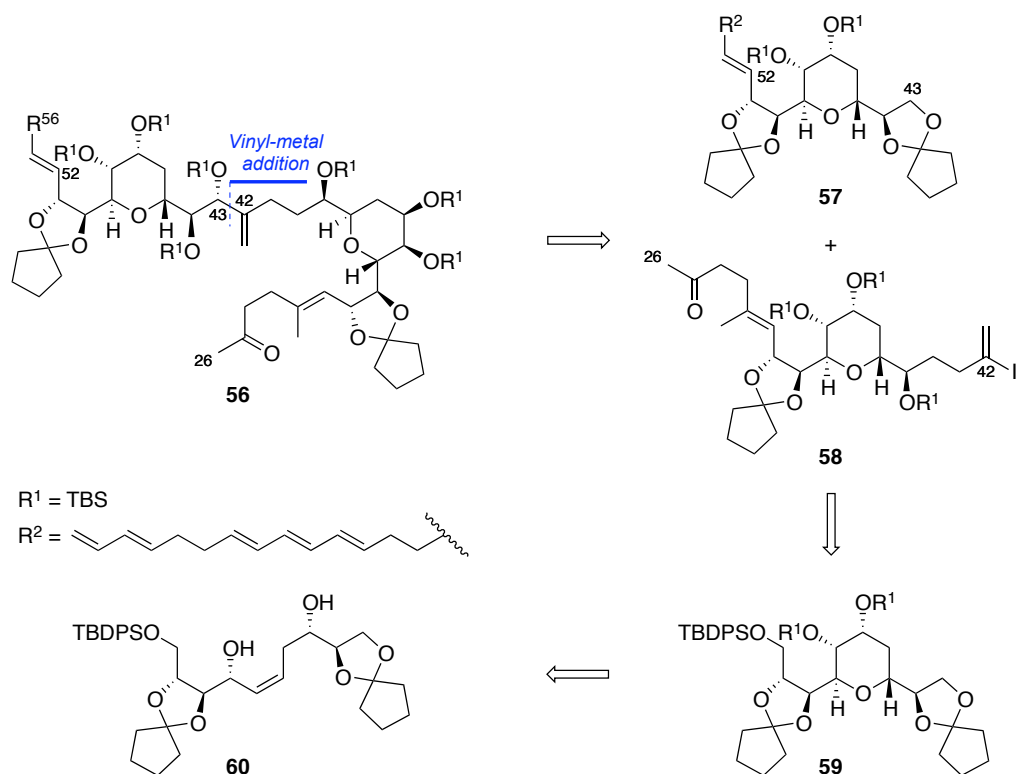
Scheme 5.4.3: Synthesis of the C43-C67 Fragment



Hence, addition of triethyl orthoacetate in presence of pivalic acid at 140 °C gave, after DIBAL-H reduction, aldehyde **54** in 70% yield and successfully established the C52-C53 (*E*)-alkene. Installation of the polyolefin chain under Horner-Wadsworth-Emmons conditions was met with moderate success. Addition of lithiated phosphonate **55a** proceeded with good *E/Z* control (>90:10), but in very poor yield due to the low reactivity of the phosphonate and oligomerisation of the aldehyde. Conversely, the more reactive diethyl phosphate **55b** gave higher yield, but diminished selectivity (*E/Z* = 86:14).

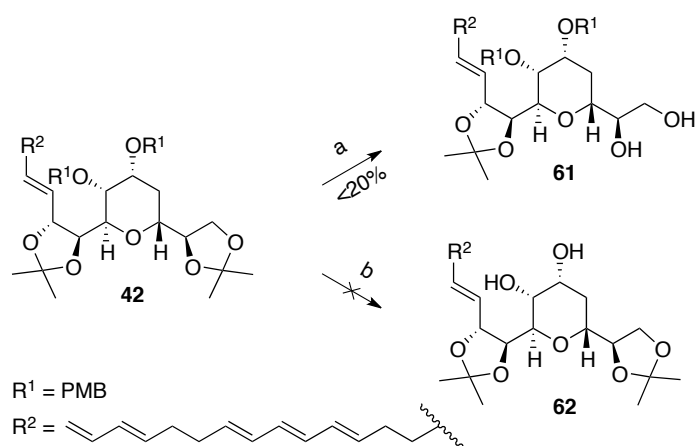
The same group later reported a revised strategy towards the C26-C42 and C43-C67 fragments of amphidinol 3 (Scheme 5.4.4).³³ While the major disconnection remained at the same position, the protecting group choice was refined.

Scheme 5.4.4: *Revised Retrosynthetic Analysis*



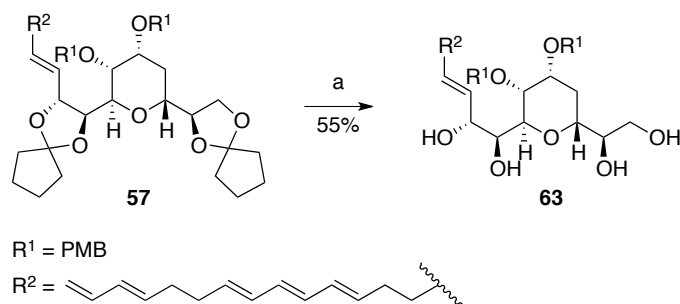
The main reasons for alterations were difficulties encountered during the deprotection studies of **42** (Scheme 5.4.5). Attempts to chemoselectively cleave the terminal acetonide in **42** using various Lewis and protic acids were inefficient (<20% yield) and accompanied by decomposition. Additionally, deprotection of the *bis*-PMB ether could not be accomplished in the presence of the polyene due to competitive oxidation of the triene moiety.

Scheme 5.4.5: *Deprotection Studies of the Polyene Fragment 42*



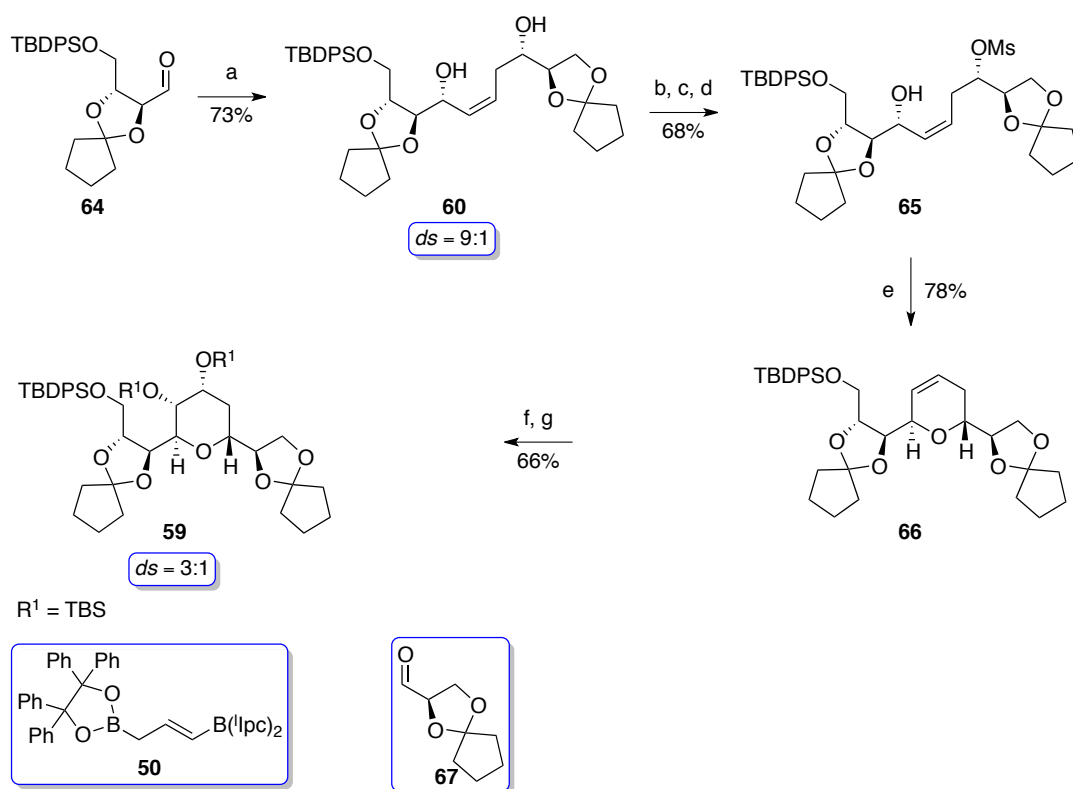
Gratifyingly, model studies suggested that cyclopentylidene ketals could be a viable replacement for the acetonide groups owing to their greater acid lability under mild conditions (Scheme 5.4.6).³⁴

Scheme 5.4.6: *Model Deprotection of Cyclopentylidene Ketals*



The common THP fragment **59** was prepared using a slightly modified procedure to that described previously (Scheme 5.4.7). Double allylboration reaction of aldehydes **64** and **67** afforded 1,5-*syn* diol **60** in good yield and selectivity (*ds* = 9:1). Formation of the methanesulfonate of homoallylic alcohol **60** was achieved using a sequence of TES protection of the allylic alcohol, mesylation and silyl deprotection. Dehydrative cyclisation of **65** gave dihydropyran **66** in 78% yield. Sharpless dihydroxylation^{29,30} of the latter, followed by TBS protection gave *bis*-silyl ether **59** in 66% overall yield.

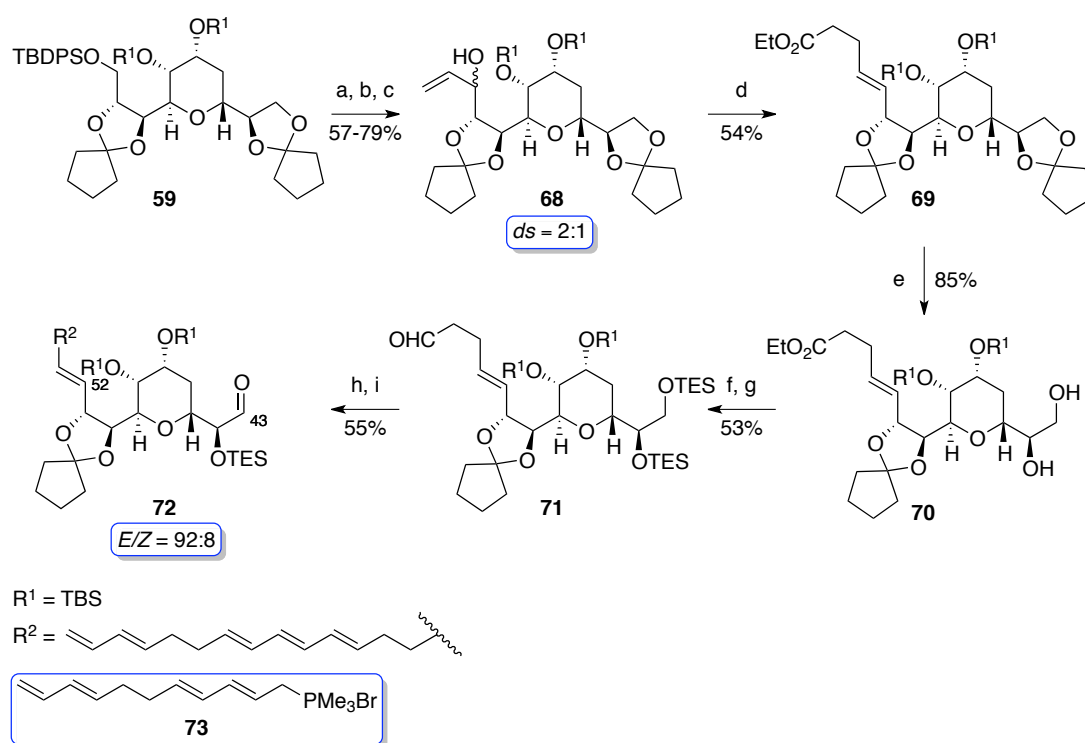
Scheme 5.4.7: *Synthesis of the Common THP Fragment 59 via Double Allylboration*



Reaction conditions: a) **50**, DCM, -78°C , then **67**, DCM, -78°C to RT, *ds* = 9:1, 73%. b) TESCl, imid, *cat.* DMAP, DCM/DMF (1:1), -78°C , 79%. c) MsCl, Et₃N, *cat.* DMAP, DCM, 0°C . d) AcOH, H₂O/THF (1:1), RT, 86% over 2 steps. e) KO^tBu, ^tAmOH, 0°C , (0.03 M), 78%. f) *cat.* K₂OsO₂(OH)₄, *cat.* DHQD-IND, K₃Fe(CN)₆, K₂CO₃, ^tBuOH/H₂O (1:1), 0°C , *ds* = 3:1, quant., 74% of desired isomer. g) TBSOTf, 2,6-lutidine, DCM, -40°C to RT, 89%.

Construction of the polyene fragment from the common intermediate **59** is described in Scheme 5.4.8. Chemoselective deprotection of primary TBDPS ether was achieved under mild conditions with TAS-F.³⁵ Oxidation and vinylmagnesium bromide addition, succeeded by Johnson-Claisen ortho ester rearrangement³² of the intermediate alcohol **68** furnished ester **69**. Mild and selective removal of the terminal cyclopentylidene ketal was achieved using $\text{FeCl}_3/\text{SiO}_2$.³⁶ Notably, these conditions were incompatible with the polyene hence, requiring its installation to be postponed to a later stage in the synthesis. Diol **70** was masked as *bis*-TES ether and the ester functionality was selectively reduced to an aldehyde using DIBAL-H.

Scheme 5.4.8: Synthesis of the C43-C67 Fragment 72



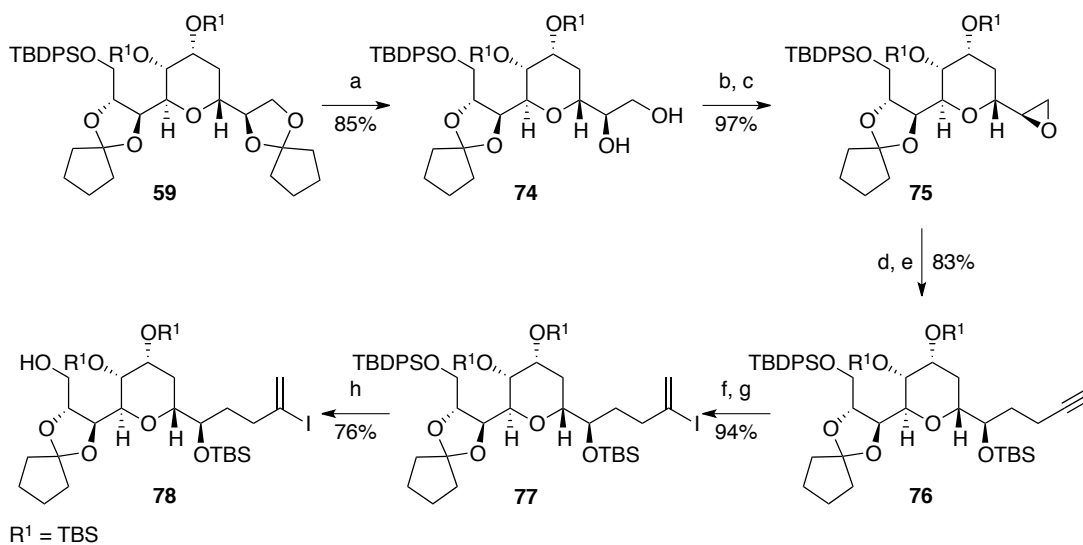
Reaction conditions: a) TAS-F, DMF, 0 °C, 70-96%. b) $(\text{COCl})_2$, DMSO, Et_3N , DCM, -78 °C to RT. c) VinylMgBr, THF, 0 °C, $ds = 2:1$, 82% over 2 steps. d) $(\text{EtO})_3\text{CMe}$, pivalic acid, xylene, 140 °C, 54%. e) $\text{FeCl}_3/\text{SiO}_2$, CHCl_3 , RT, 85%. f) TESCl, imid, DMAP, DCM/DMF (1:1), 0 °C, 75%. g) DIBAL-H, DCM, -78 °C, 70%. h) **73**, $n\text{BuLi}$, THF/HMPA (2:1), -78 °C, then **71**, THF, -78 °C to 0 °C, $E/Z = 92:8$, 75%. i) $(\text{COCl})_2$, DMSO, Et_3N , DCM, -78 °C to -40 °C, 73%.

Next, improved olefination conditions were applied, which involved addition of Wittig ylide, derived from the phosphonium salt **73**, to produce the polyene

fragment with 92:8 *E/Z* selectivity. Finally, Swern oxidation of the primary TES ether³⁷ afforded aldehyde **72** as an advanced C43-C67 fragment of amphidinol 3.

The synthetic sequence leading to the C26-C42 fragment **58** began with deprotection of the common fragment **59** using $\text{FeCl}_3/\text{SiO}_2$ (Scheme 5.4.9).³⁶ Selective tosylation of the primary alcohol using Martinelli's protocol³⁸ and formation of epoxide **75** proceeded in excellent overall yield (97%). Subsequent epoxide opening with dilithiopropyne³⁹ and TBS protection of the newly formed alcohol furnished alkyne **76**, ready for the crucial installation of the vinyl iodide moiety. Construction of **77** was secured *via* stannylalumination/iodination⁴⁰ sequence in excellent 94% yield. Lastly, selective removal of the primary TBDPS ether afforded alcohol **78** in good yield.

Scheme 5.4.9: *Synthesis of the Vinyl Iodide 78*

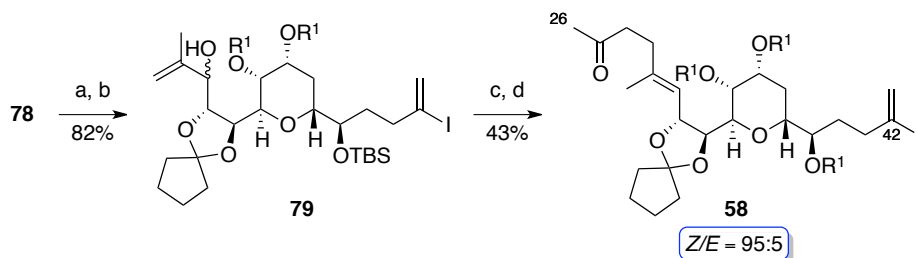


Reaction conditions: a) $\text{FeCl}_3/\text{SiO}_2$, CHCl_3 , RT, 85%. b) *cat.* $\text{Bu}_2\text{Sn}(\text{OMe})_2$, TsCl , Et_3N , DCM. c) NaH , THF, 0 °C to RT, 97%. d) 1,3-Dilithiopropyne, $\text{Et}_2\text{O}/\text{hexane}$, -78 °C. e) TBSOTf , 2,6-lutidine, -40 °C to 0 °C, 83% over 2 steps. f) $\text{Bu}_2\text{SnAlEt}_2$, *cat.* CuCN , THF, -30 °C. g) NIS , DCM, RT, 94% over 2 steps. h) TAS-F , DMF, RT, 76%.

The completion of fragment **58** was achieved as follows (Scheme 5.4.10). Oxidation of the primary alcohol under Swern conditions,³¹ followed by isopropenylmagnesium bromide addition furnished a 2:1 mixture of allylic

alcohols **79**. Formation of the vinyl ether and subsequent Claisen rearrangement⁴¹ afforded the C26-C42 segment of amphidinol 3 in 43% yield over 2 steps and excellent selectivity ($E/Z = 95:5$).

Scheme 5.4.10: Synthesis of the C26-C42 Fragment **58**

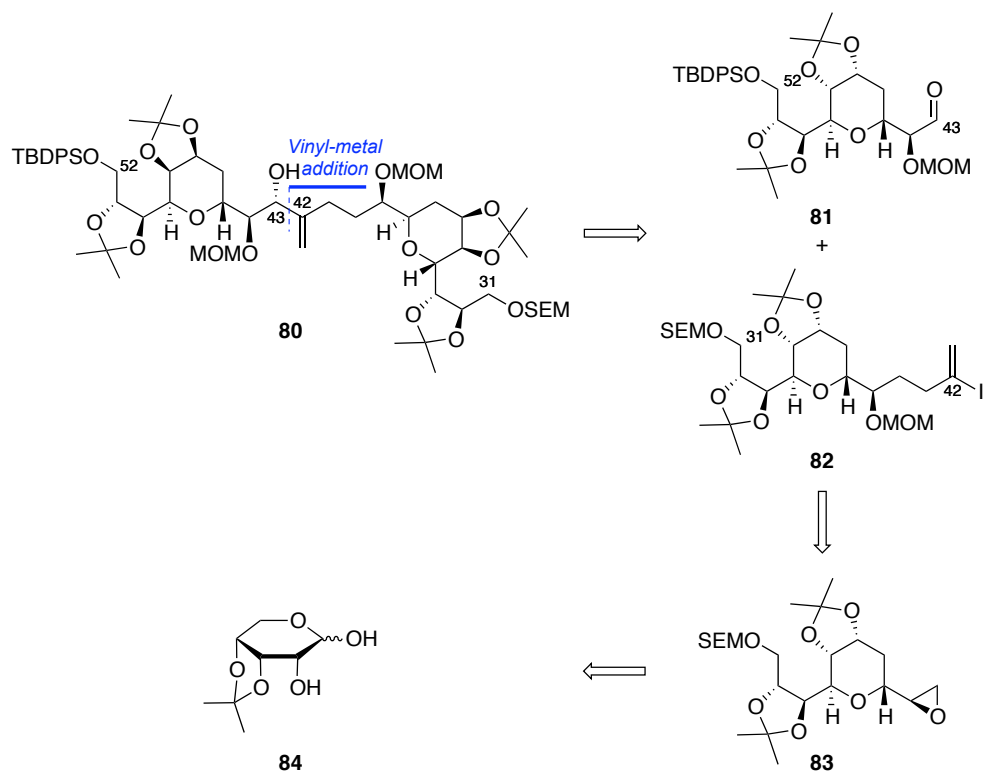


Reaction conditions: a) $(\text{COCl})_2$, DMSO, Et_3N , DCM, -78°C to RT. b) Isopropenylmagnesium bromide, THF, 0°C , 82% over 2 steps. c) 2-Methoxypropene, PPTS. d) $\text{C}_6\text{H}_5\text{Cl}$, cat. K_2CO_3 , 170°C , $E/Z = 95:5$, 43%.

To conclude, the route developed by Roush and co-workers offered an elegant and highly effective synthesis of the common THP fragment of amphidinol 3 in 7 longest linear steps with a remarkable 26% yield. The revised synthetic strategy improved the E/Z selectivity of the Wittig olefination and furnished the C43-C67 polyene fragment in 16 steps and 2.3% overall yield, while the C26-C42 fragment was prepared in 19 steps and 4.3% yield (longest linear sequence).

5.5 Paquette's Synthesis of C31-C52 and C44-C67 Fragments of Amphidinol 3

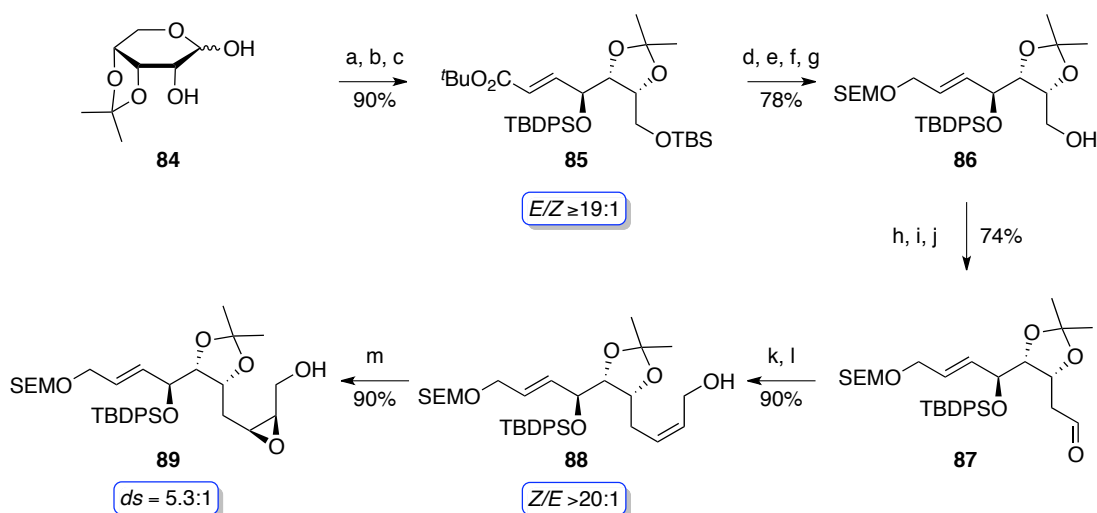
The Paquette group had also made an important contribution towards overcoming the synthetic challenge of amphidinol 3.^{42,43} Their approach had an analogous strategic disconnection and a somewhat similar common THP fragment when compared to reports of Rychnovsky^{1,9} and Roush^{25,33} (Scheme 5.5.1). However, in contrast with other strategies the elaboration of the common intermediate **83** was achieved from a readily available sugar.

Scheme 5.5.1: *Paquette's Retrosynthetic Analysis of the bis-THP Fragment*

In their first report, the synthesis of the THP intermediate **92** and its union with the polyene segment was demonstrated.⁴² The synthesis of epoxy alcohol **89** commenced from 3,4-*O*-isopropylidene- β -*D*-ribofuranose **84** (Scheme 5.5.2).⁴⁴ Homologation of **82** with a carbonyl stabilised Wittig reagent,⁴⁵ followed by silylation afforded α,β -unsaturated ester **85** as a single geometrical isomer. Formation of **86** was achieved with a series of steps that involved ester reduction to an alcohol, SEM protection and chemoselective primary TBS ether cleavage using NBS in wet DMSO (78% yield over 4 steps).⁴⁶ Next, Dess-Martin oxidation¹⁸ and one-carbon homologation of the resultant aldehyde, *via* Wittig olefination with methoxymethylene(triphenyl)phosphorane,⁴⁷ followed by mercuration-reductive demercuration⁴⁸ furnished aldehyde **87** in good yield. Ensuing conversion of the latter into the (*Z*)-allylic alcohol **88** was readily achieved using Still-Gennari modified HWE coupling with trifluoroethylphosphono ester⁴⁹ in excellent yield and

selectivity ($Z/E > 20:1$). Ester reduction and Sharpless asymmetric epoxidation⁸ afforded the required epoxy alcohol **89** in 90% yield as a 5.3:1 mixture of diastereoisomers.

Scheme 5.5.2: *Synthesis of the Epoxy Alcohol 89*

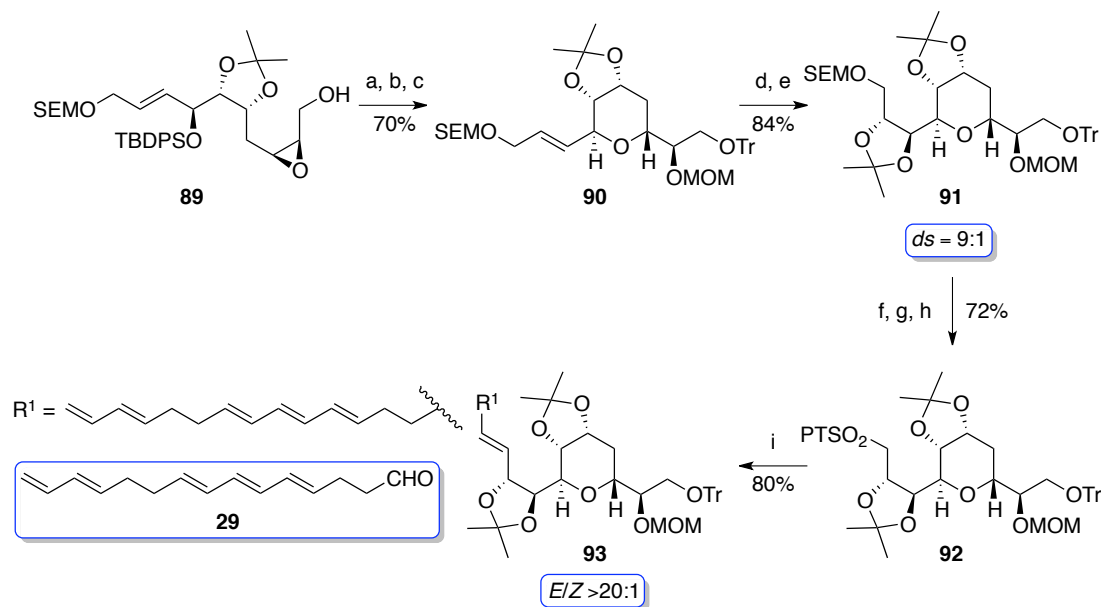


Reaction conditions: a) $\text{Ph}_3\text{PCHCO}_2^t\text{Bu}$, DMF/dioxane (1:1), 75 °C, $E/Z \geq 19:1$, 90%. b) TBSCl, Et_3N , DMAP, quant. c) TBDPSCl, imid, DMAP, DMF, 50 °C, quant. d) DIBAL-H, DCM, -78 °C. e) NaBH_4 , THF/MeOH, 95% over 2 steps. f) SEMCl, DIPEA, Bu_4NI , 99%. g) NBS, DMSO/ H_2O , RT, 93%. h) DMP, Py, DCM, 99%. i) Ph_3PCHOMe , THF, 99%. j) $\text{Hg}(\text{OAc})_2$, then NaBH_4 , THF/ H_2O , 0 °C, 75%. k) $(\text{CF}_3\text{CH}_2\text{O})\text{POCH}_2\text{CO}_2\text{Me}$, 18-crown-6, KHMDS, $Z/E > 20:1$, 91%. l) DIBAL-H, DCM, -78 °C, 99%. m) $\text{Ti}(\text{O}^i\text{Pr})_4$, $^t\text{BuO}_2\text{H}$, (-)-DIPT, 4 Å MS, DCM, $ds = 5.3:1$, 82%.

Next, the key task was the formation of the THP ring from epoxy alcohol precursor (Scheme 5.5.3). This was achieved in one-pot during secondary TBDPS ether cleavage with TBAF, which proceeded with concomitant 6-*exo*-tet cyclisation. Regioselective tritylation of the diol,⁵⁰ followed by MOMCl protection gave intermediate **90** ready for the asymmetric dihydroxylation. Application of Sharpless conditions²⁹ resulted in the corresponding diol with 9:1 selectivity, which was protected as its acetonide **91**. Formation of the Julia-Kocienski olefination precursor was achieved by removal of the primary SEM ether, Mitsunobu reaction with PTSH and oxidation with molybdate-hydrogen peroxide complex.²² With sulfone **92** in hand the olefination reaction with polyene aldehyde **29** was evaluated. Remarkably,

the coupling product **93** was obtained in excellent yield and selectivity ($E/Z > 20:1$) using KHMDS as base and THF as solvent. This result is in great contrast with findings of Rychnovsky *et al.* who reported the similar reaction of *bis*-THP sulfone **26** and aldehyde **29** to be non-selective and low yielding (Scheme 5.2.7).⁹

Scheme 5.5.3: Elaboration of the THP and its Union with the Polyolefin

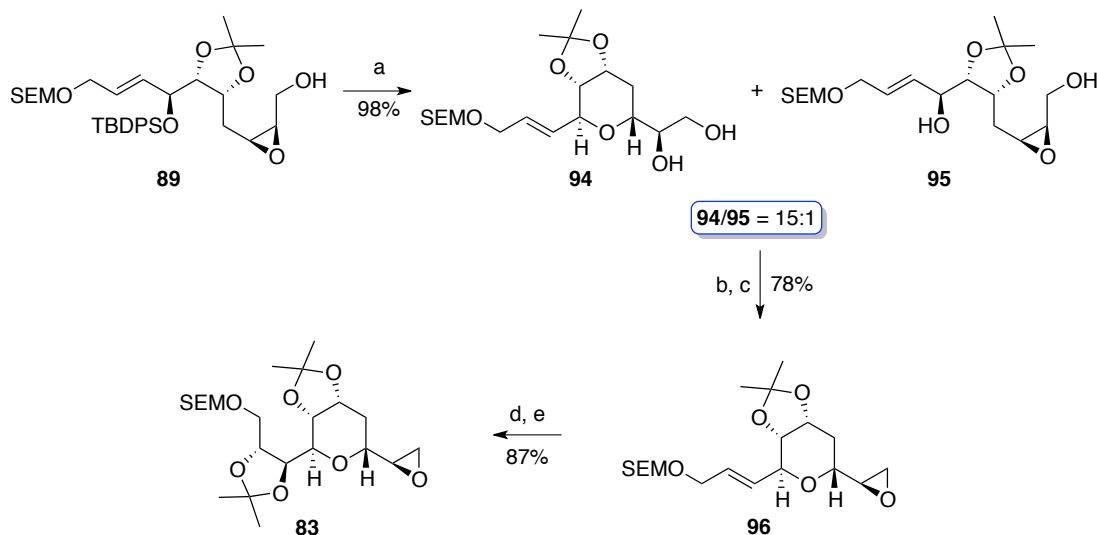


Reaction conditions: a) TBAF, THF, RT, 84%. b) TrCl, Py, 35 °C, 89%. c) MOMCl, DIPEA, 40 °C, CHCl₃, 94%. d) AD-mix-β, *t*BuOH/H₂O, 98%, *ds* = 9:1. e) 2,2-DMP, PPTS, 86%. f) TBAF, THF, 55 °C, 90%. g) PTSH, DIAD, Ph₃P, THF. h) Mo₇O₂₄(NH₄)₆·4H₂O, H₂O₂, 80% over 2 steps. i) **29**, KHMDS, THF, $E/Z > 20:1$.

In 2007, the same group reported a revised strategy to the synthesis of the *bis*-THP C31-C52 core of amphidinol **3**.⁵¹ In their earlier synthesis, the formation of the THP ring using a 6-*exo*-tet cyclisation of **89** proceeded with good yield (Scheme 5.5.4). However, the scale up procedure was complicated by the lack of cyclisation during silyl ether deprotection (Scheme 5.5.4). The problem was circumvented by subjecting the mixture of **94** and **95** to selective dibutyltin(IV) oxide mediated tosylation³⁸ of primary alcohols and methanolic K₂CO₃ induced cyclisation to afford epoxide **96** in excellent overall yield. The formation of the common THP fragment

83 was then achieved *via* asymmetric dihydroxylation with AD-mix- β ,²⁹ followed by acetonide formation using 2,2-dimethoxypropane.

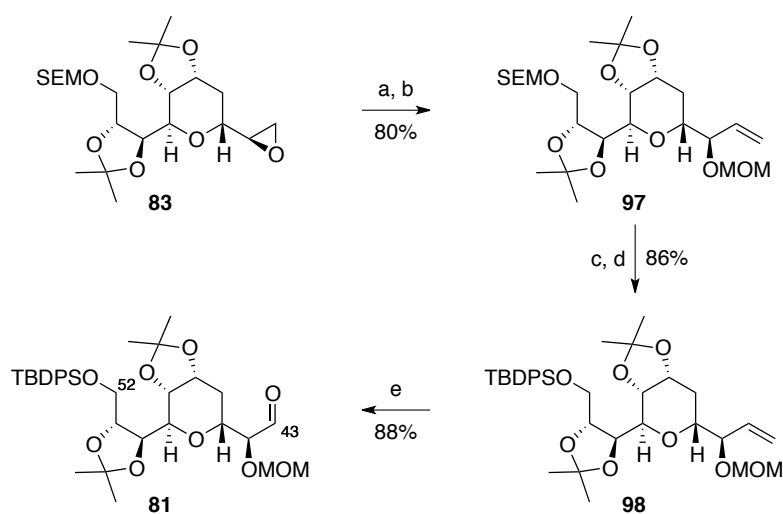
Scheme 5.5.4: Synthesis of the Common THP Fragment **83**



Reaction conditions: a) TBAF, THF, RT, **94/95** = 15:1, 0 °C, 91%. b) TsCl, Et₃N, cat. Bu₂SnO, RT, 91%. c) K₂CO₃, MeOH, 0 °C, 86%. d) AD-mix- β , ^tBuOH/H₂O (1:1), 0 °C, 97%. e) 2,2-DMP, cat. PPTS, RT, 90%.

With the common THP fragment in hand, elaboration to the C31-C52 segment of amphidinol **3** was carried out (Scheme 5.5.5).

Scheme 5.5.5: Synthesis of the C43-C52 Fragment

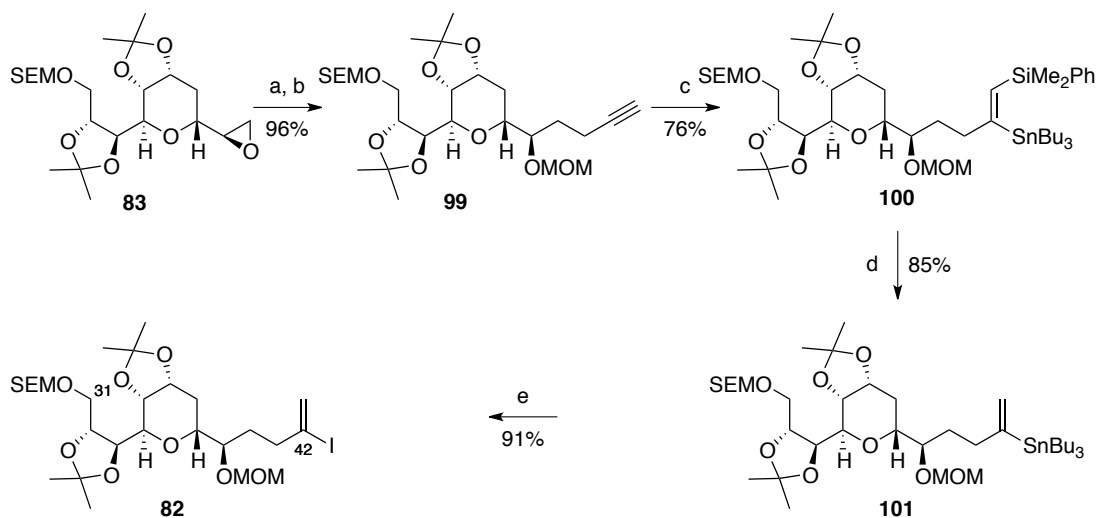


Reaction conditions: a) Me₃SiLi, ⁿBuLi, THF, -10 °C, 87%. b) MOMCl, DIPEA, CHCl₃, 40 °C, 92%. c) TBAF, THF, 4 Å MS, 55 °C, 86%. d) TBDPSCl, imid, DMAP, DCM, RT, 89%. e) cat. OsO₄, NaIO₄, THF/pH 7 buffer (1:1), RT, 88%.

Epoxide opening of **83** with a sulfonium ylide,⁵² followed by MOM protection resulted in terminal alkene **97**. Protecting group exchange and Johnson-Lemieux oxidation¹⁷ furnished aldehyde **81**, which constitutes the C43-C52 fragment of AM3.

The synthesis of the C31-C42 vinyl iodide **82** is shown in Scheme 5.5.6. Addition of allenylmagnesium bromide to epoxide **83** and protection of resultant alcohol as a MOM ether afforded alkyne **99** in 96% yield over 2 steps. Elaboration of the alkyne to the vinyl iodide **82** was achieved in a sequence involving silylstannation,⁵³ hydrolysis of the dimethylphenylsilyl intermediate **100** and tin-iodine exchange using I₂. It is noteworthy that the choice of silyl group was crucial for smooth formation of the terminal alkene. The use of the conventional TMS group led to concomitant removal of SEM group under TBAF conditions.

Scheme 5.5.6: Synthesis of the C31-C42 Fragment

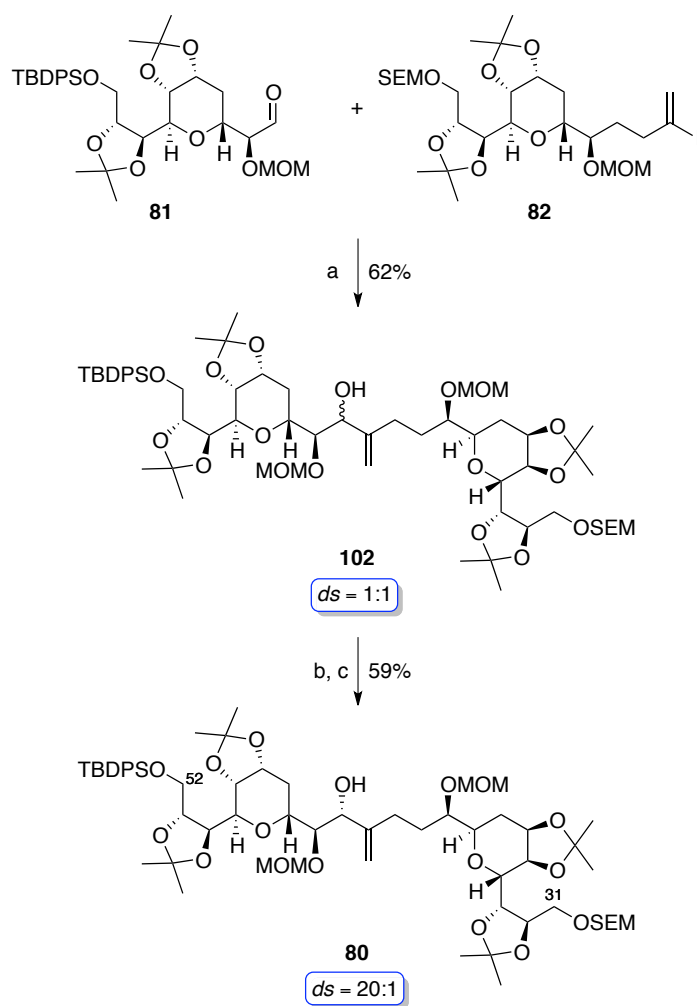


Reaction conditions: a) Propargyl bromide, Mg, *cat.* HgCl₂, -78 °C to RT, quant. b) MOMCl, DIPEA, CHCl₃, 40 °C, 96%. c) ⁿBu₃SnSiMe₂Ph, *cat.* Pd(PPh₃)₄, 35 °C, 76%. d) TBAF, DMSO, 80 °C to RT, 71%. e) I₂, DCM, 0 °C, 91%.

Strategic coupling of the THP fragments is described in Scheme 5.5.7. Addition of vinyl iodide **82** to aldehyde **81** was achieved under Nozaki-Hiyama-Kishi conditions⁵⁴ and provided **102** in 62% yield as a 1:1 mixture of isomers.

It should be noted that coupling of the corresponding lithium reagent, derived from transmetalation of the stannane, was extremely sluggish (7% yield). This result is opposed to the report of Rychnovsky and co-workers who successfully used this reaction in their coupling strategy (*vide supra*). Finally, the completed C31-C52 fragment **80** was obtained after oxidation and enantioselective CBS reduction.⁵⁵

Scheme 5.5.7: Elaboration of the bis-THP fragment **80**



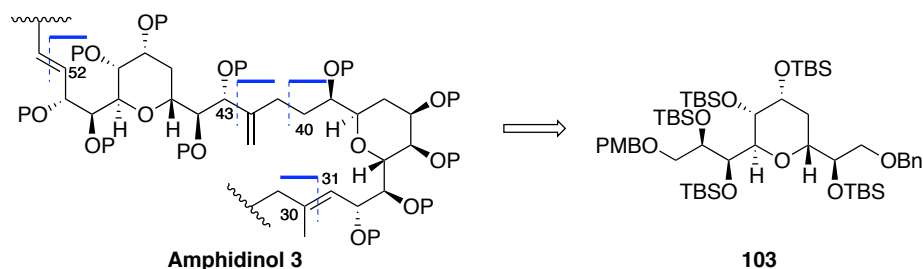
In summary, Paquette and co-workers have developed a rather linear (18 steps from the known compound) but quite effective route (28% overall yield) to the common THP intermediate of amphidinol 3. The unique feature of their approach is

the application of a sugar derivative as the starting material, which obviated the need for stereoselective dihydroxylation of the pyran ring, which is known to be challenging. Other highlights include the NHK coupling and CBS-reduction to access *bis*-THP segment and application of Julia olefination for the union of the polyene with the pyran fragment.

5.6 Oishi's Synthesis of the Common THP Fragment of Amphidinol 3

In 2009, Oishi, Murata and Kanemoto reported their approach towards the stereoselective synthesis of the common THP fragment of amphidinol 3.⁵⁶ The authors envisaged that the *bis*-THP system of AM3 could arise by positioning disconnections at the (*E*)-olefinic regions (Scheme 5.6.1). This in turn could be traced to the common intermediate **103**, which corresponds to the C31-C40/C43-C52 fragments of the natural product.

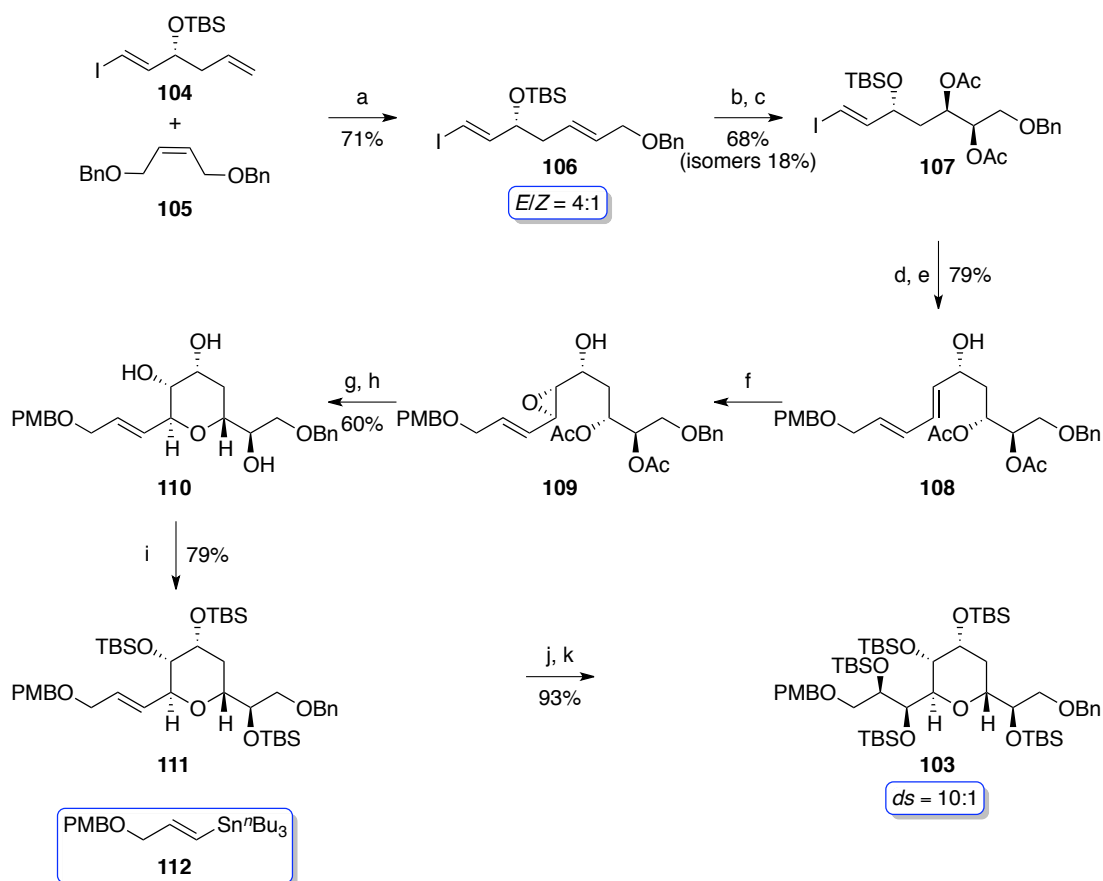
Scheme 5.6.1: Oishi's Retrosynthetic Analysis of AM3



As shown in Scheme 5.6.2, the synthesis of the common intermediate **103** commenced with the chemoselective cross-metathesis of **104**⁵⁷ (available through enzymatic resolution) and **105**, mediated by Grubbs 2nd generation catalyst,⁵⁸ to afford **106** with modest selectivity (*E/Z* = 4:1). Sharpless dihydroxylation²⁹ of the more electron-rich olefin, followed by acetylation furnished **107** (68% yield), which was separated from unwanted isomers. Mogita-Kosugi-Stille coupling⁵⁹ with

stannane **112**⁶⁰ gave (*E,E*)-diene. The latter was desilylated with HF·Py in good overall yield (88%). Formation of the THP ring was achieved by performing Sharpless epoxidation of **108**,⁸ acetate removal and subsequent 6-*endo*-tet cyclisation⁶¹ of the resultant epoxy vinyl alcohol (60% yield over 3 steps). Treatment of **110** with TBSOTf/2,6-lutidine effected protection of the triol. Finally, asymmetric dihydroxylation²⁹ and silyl protection installed the last stereocentres in the molecule with excellent stereocontrol (*ds* = 10:1).

Scheme 5.6.2: *Synthesis of the C31-C40/C43-C52 Fragment of AM3*



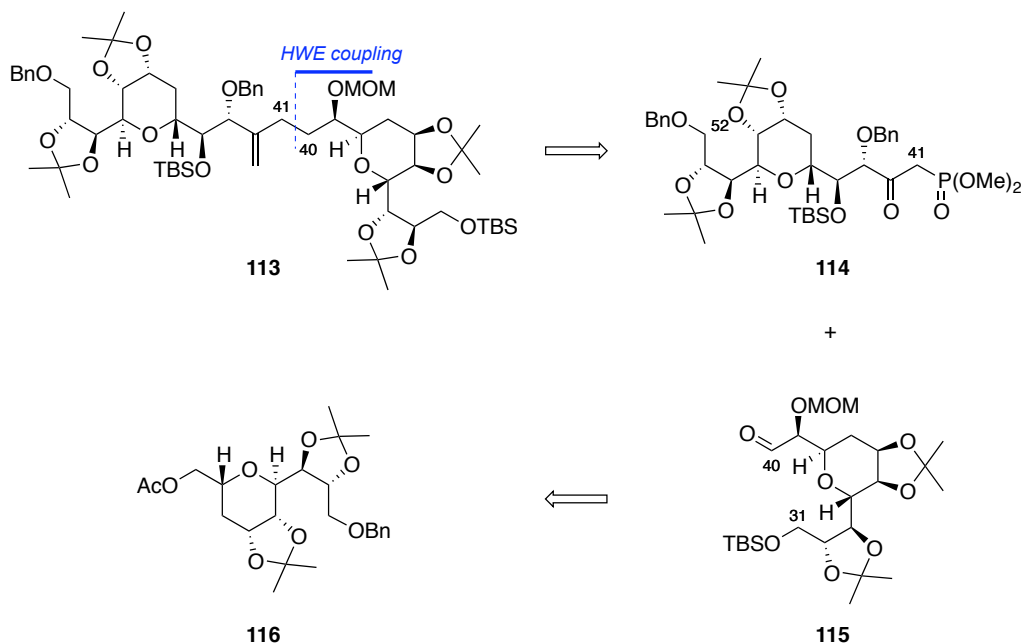
Reaction conditions: a) *cat.* G-II, DCM, 40 °C, *E/Z* = 4:1, 71%. b) AD-mix- β , ^tBuOH/H₂O (1:1), 0 °C, 68% (isomers 18%). c) Ac₂O, Py, *cat.* DMAP, 0 °C to RT, 99%. d) **112**, *cat.* PdCl₂(MeCN)₂, DMF, 0 °C to RT, 92%. e) HF·Py, THF, 0 °C to 35 °C, 86%. f) *cat.* Ti(OⁱPr)₄, TBHP, *cat.* (–)-DET, 4Å MS, –20 °C, DCM. g) K₂CO₃, MeOH, 0 °C. h) *cat.* PPTS, DCM, 0 °C, 60% over 3 steps. i) TBSOTf, 2,6-lutidine, DCM, 0 °C, 79%. j) AD-mix- β , ^tBuOH/H₂O (1:1), 0 °C, *ds* = 10:1, 97%. k) TBSOTf, 2,6-lutidine, DCM, 0 °C to RT, 96%.

In summary, Oishi and co-workers developed a concise synthesis of the THP intermediate of amphidinol 3 in 16% yield over 11 longest linear steps. The highlights of their route include chemoselective cross-metathesis, regioselective dihydroxylation and pyran formation *via* 6-*endo*-tet cyclisation of an epoxy vinyl alcohol.

5.7 Crimmins' Synthesis of the *bis*-THP Fragment of Amphidinol 3

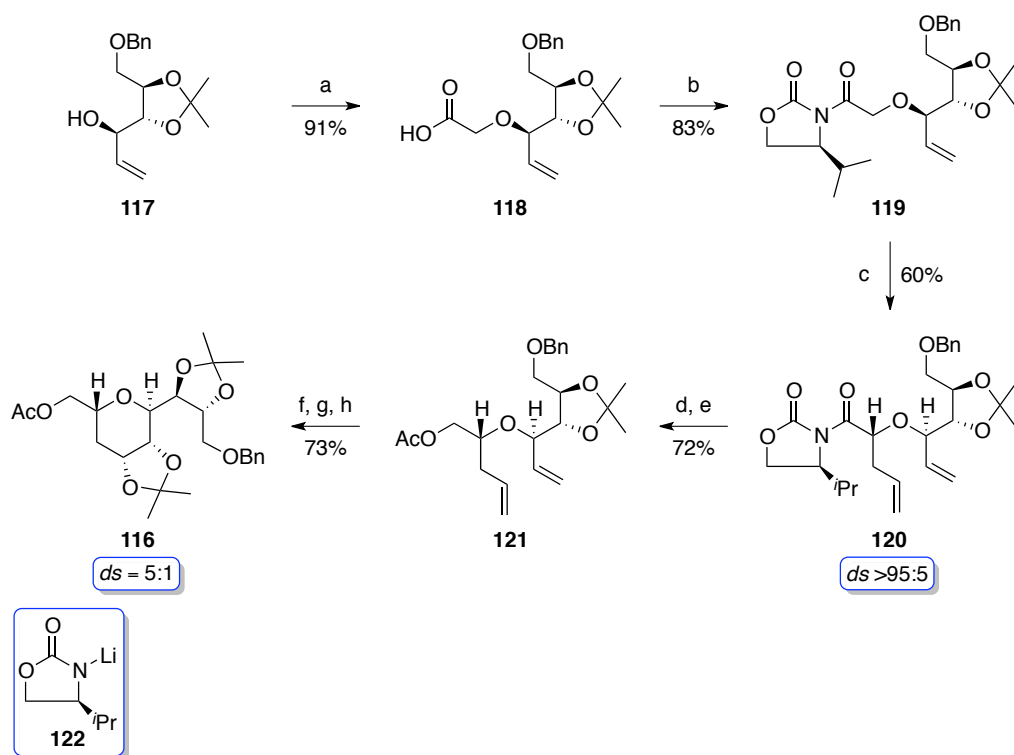
In 2010, Crimmins and co-workers reported the synthesis of the *bis*-THP segment of amphidinol 3.⁶² They planned to disconnect fragment **113** at C40-C41 to deliver two THP cores of similar complexity, each of which could be prepared in a concise manner from the common intermediate **116** (Scheme 5.7.1). The latter could be obtained using the asymmetric glycolate alkylation/ring-closing metathesis strategy developed by the same group.⁶³

Scheme 5.7.1: *Crimmins' Retrosynthetic Analysis of the bis-THP Fragment*



The synthesis of the common THP fragment **116** commenced from known allylic alcohol **117**, available *via* Felkin-Ahn vinylation of **7** as 9:1 mixture of diastereoisomers (Scheme 5.7.2).² Alkylation with bromoacetic acid gave **118**, which was coupled with the valine-derived chiral auxiliary **122** to provide *N*-glycolyl oxazolidinone **119** in 83% yield. Diastereoselective alkylation of the sodium enolate of **119** with allyl iodide installed the crucial stereocentre at C45 with excellent stereocontrol (*ds* >95:5).⁶³ The chiral auxiliary was removed under reductive conditions, followed by the acetylation of resultant primary alcohol (72% yield). The formation of **116** set the stage for the RCM/dihydroxylation sequence.

Scheme 5.7.2: Synthesis of the Common THP Fragment 116

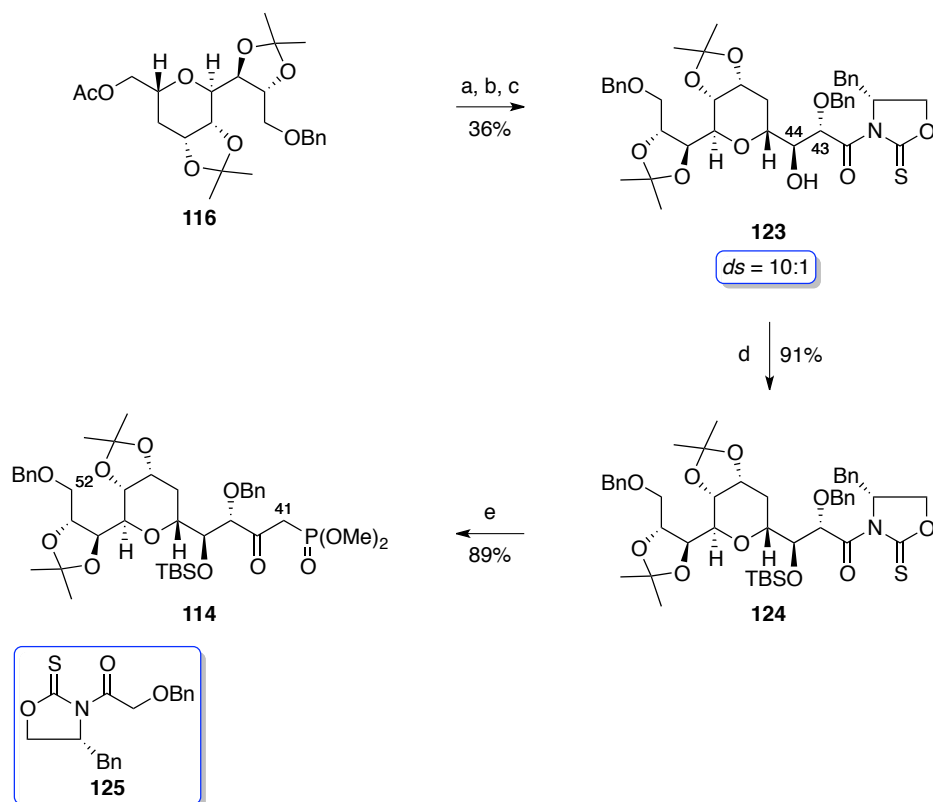


Reaction conditions: a) BrCH₂CO₂H, NaH, THF/DMF (3:1), 0 °C to RT, 91%. b) PivCl, Et₃N, THF, -78 °C to RT, then **122**, THF, -78 °C to RT, 83%. c) NaHMDS, THF, allyl iodide, -78 °C to -65 °C, 60%. d) NaBH₄, THF/H₂O (4:1), 0 °C. e) Ac₂O, Py, *cat.* DMAP, DCM, RT, 72% over 2 steps. f) *cat.* G-I, DCM, 40 °C. g) NaIO₄, *cat.* YbCl₃, EtOAc/MeCN/H₂O (3:3:1), 0 °C, *ds* = 5:1. h) 2,2-DMP, PTSA, RT, 73% over 3 steps.

By taking advantage of ruthenium able to act as oxidant, the RCM reaction and dihydroxylation with $\text{NaIO}_4/\text{YbCl}_3$ were carried out in one-flask. The latter Lewis acid was necessary to reduce the unwanted over-oxidation of the diol. Subsequent formation of the acetonide afforded **116** in 73% overall yield and good selectivity ($ds = 5:1$).

With the common fragment **116** in hand, bidirectional elaboration to C41-C52 and C31-C40 segments was carried out (Scheme 5.7.3). Synthesis of the C41-C52 fragment commenced with primary acetate cleavage, Swern oxidation and *anti* glycolate aldol reaction⁶⁴ with the titanium enolate of **125** in presence of (–)-sparteine. This sequence furnished **123** in satisfactory yield and introduced the C43 and C44 stereocentres with good stereocontrol ($ds = 10:1$).

Scheme 5.7.3: Synthesis of the C41-C52 Fragment 114

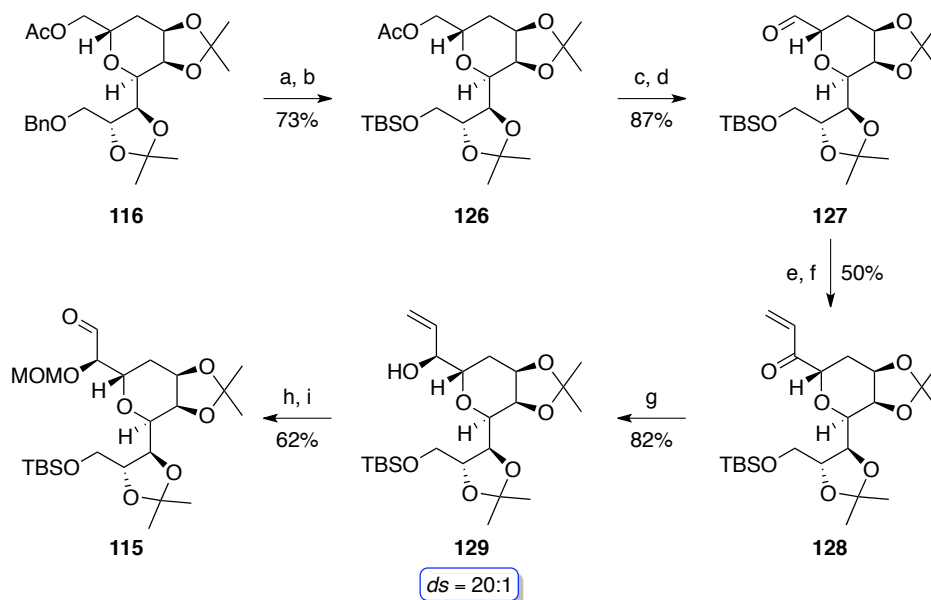


Reaction conditions: a) *cat.* K_2CO_3 , MeOH, RT, 87% b) $(\text{COCl})_2$, DMSO, Et_3N , DCM, -78°C to RT, 93%. c) **125**, TiCl_4 , (–)-sparteine, DCM, -78°C , $ds = 10:1$, 44%. d) TBSOTf, 2,6-lutidine, DCM, -78°C to 0°C , 91%. e) $\text{MePO}(\text{OMe})_2$, $n\text{BuLi}$, THF, -78°C , 89%.

Conversion of **123** into the β -ketophosphonate **114** was then secured in two steps by TBS protection of the secondary alcohol in **123**, followed by addition of lithiated dimethyl methylphosphonate.⁶⁵

The synthesis of the C31-C40 aldehyde **115** is depicted in Scheme 5.7.4. Protecting group exchange in **116** was effected by hydrogenolysis of the benzyl ether, followed by TBS protection. Primary acetate methanolysis and Swern oxidation³¹ afforded aldehyde **127**, which was next tested in the stereoselective vinylation reaction. Unfortunately, all attempts to stereoselectively add a vinyl nucleophile to **127** were encountered with low selectivity ($ds \leq 3.5:1$) thus, an oxidation/reduction sequence was carried out. Vinylmagnesium bromide addition and oxidation with Dess-Martin periodinane¹⁸ gave α,β -unsaturated ketone **128** in acceptable 50% yield. Application of Corey-Bakshi-Shibata reduction conditions⁵⁵ resulted in **129** as single stereoisomer.

Scheme 5.7.4: Synthesis of the C31-C40 Fragment 102

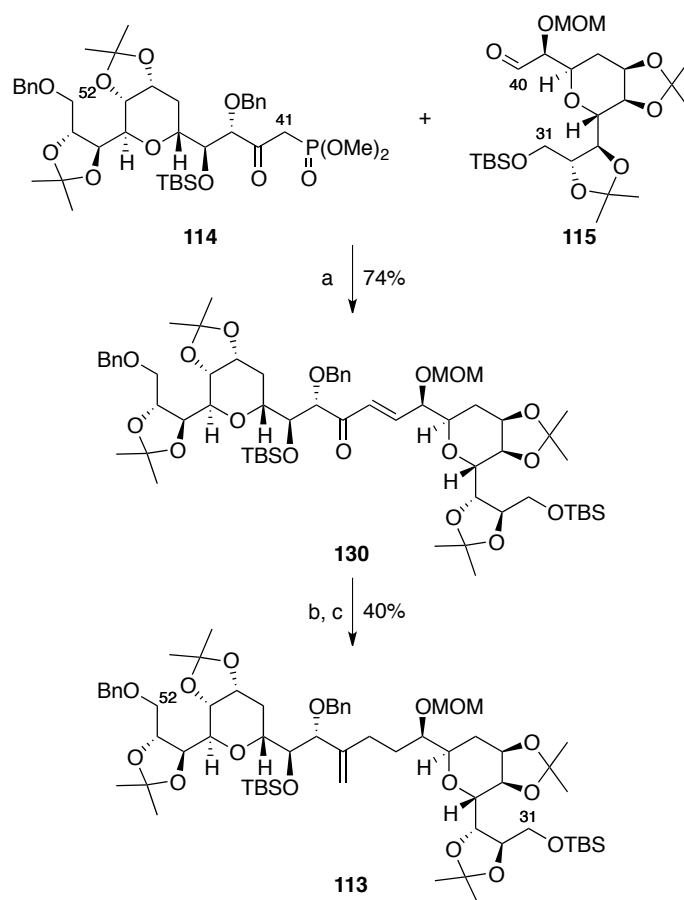


Reaction conditions: a) *cat.* Pd(OH)₂, H₂, EtOAc, RT, 87%. b) TBSCl, Et₃N, *cat.* DMAP, DCM, RT, 73% over 2 steps. c) *cat.* K₂CO₃, MeOH, RT. d) (COCl)₂, DMSO, Et₃N, DCM, -78 °C to RT, 87% over 2 steps. e) VinylMgBr, THF, 0 °C to RT. f) DMP, DCM, RT, 50% over 2 steps. g) (*R*)-Me-CBS, BH₃·DMS, DCM, 0 °C, $ds = 20:1$, 82%. h) MOMCl, DIPEA, CHCl₃, 40 °C, 94%. i) OsO₄, NaIO₄, THF/pH 7 buffer (1:1), RT, 66%.

Finally, MOM protection of the allylic alcohol and Johnson-Lemieux oxidation,¹⁷ using conditions utilised by Paquette,⁴³ afforded aldehyde **115** in 62% yield over 2 steps.

With an efficient route to both fragments of the *bis*-THP core, studies towards their union were carried out (Scheme 5.7.5). A modified HWE coupling reaction⁶⁶ between β -ketophosphonate **114** and aldehyde **115** delivered α,β -unsaturated ketone **130** in good yield. Selective 1,4-reduction of enone **130**⁶⁷ was achieved using methyl copper and DIBAL-H. Installation of the exomethylene group proved to be non-trivial and was accomplished using Tebbe's reagent⁶⁸ at elevated temperature.

Scheme 5.7.5: Synthesis of the *bis*-THP Fragment **113**

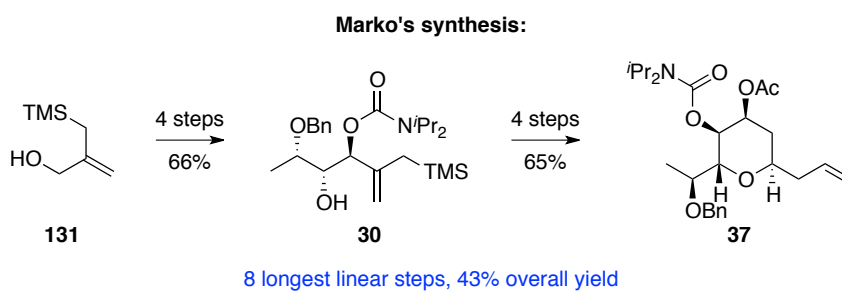
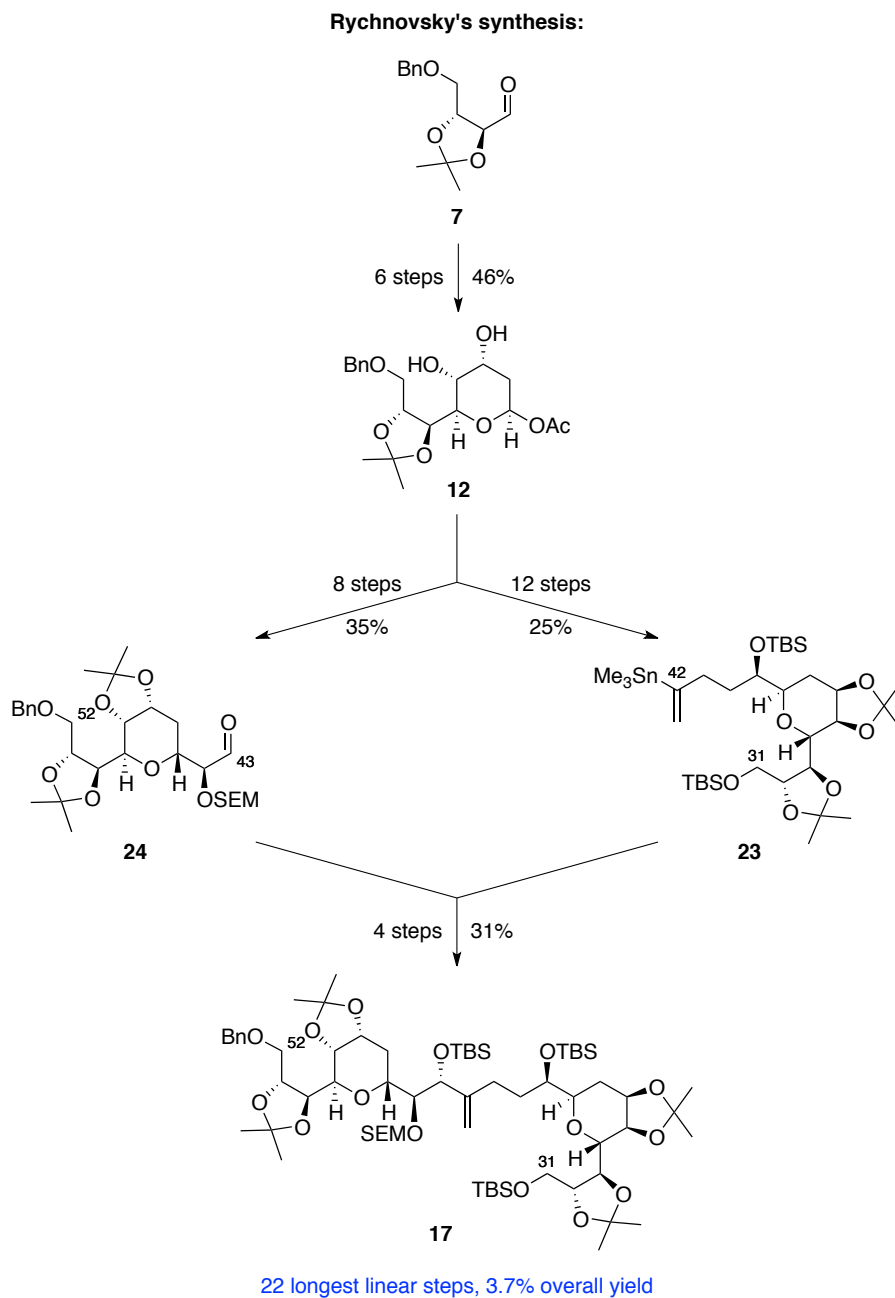


Reaction conditions: a) Ba(OH)₂, then **115**, THF/H₂O (40:1), RT, 74%. b) CuI, MeLi, HMPA, DIBAL-H, THF, -50 °C, 55%. c) Tebbe reagent, THF, toluene, 50 °C, 73%.

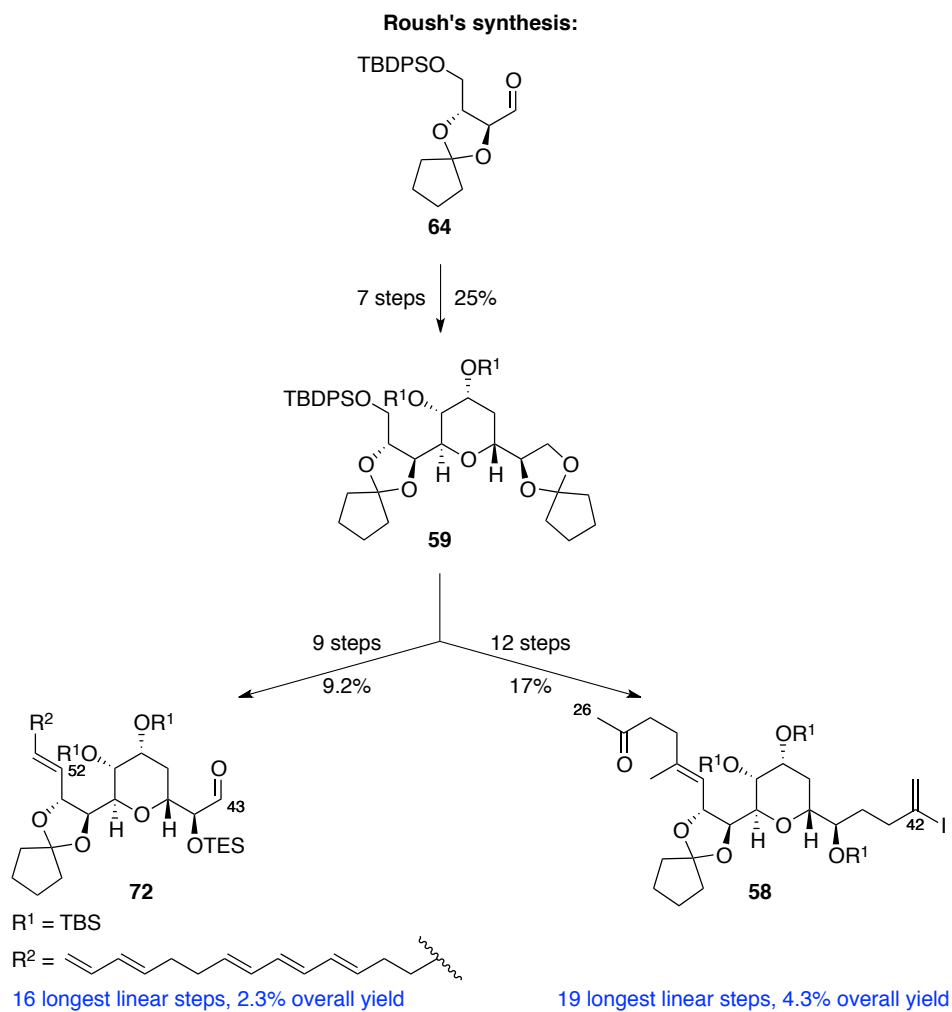
In conclusion, Crimmins and co-workers developed a convergent route to the *bis*-THP fragment of amphidinol 3, which proceeds in 20 longest linear steps and 1.1% overall yield. The synthesis of the common THP intermediate was accomplished using an asymmetric glycolate alkylation/RCM sequence, followed by substrate-controlled dihydroxylation in 8 steps and 24% yield. Using a bidirectional approach, two segments of the *bis*-THP fragment were elaborated using *anti* glycolate aldol reaction and vinylation, oxidation/stereoselective reduction sequence. The union of the latter was culminated using Horner-Wadsworth-Emmons olefination.

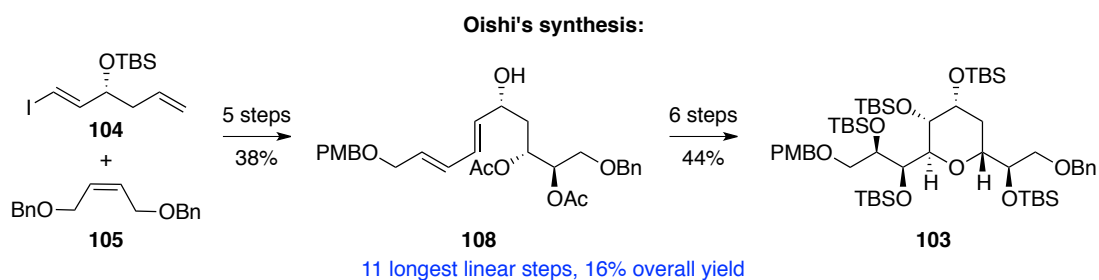
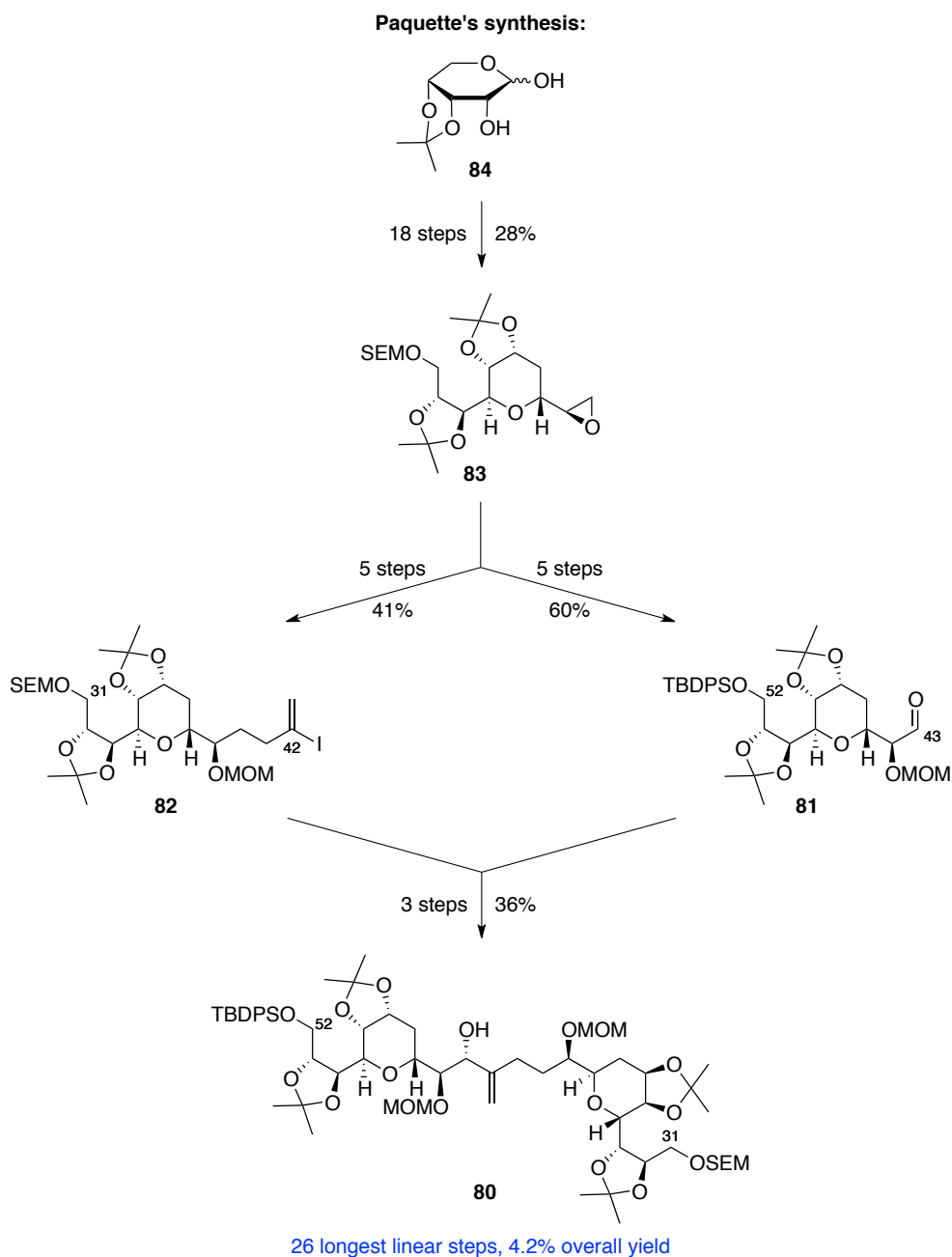
5.8 THP Fragment Syntheses Overview

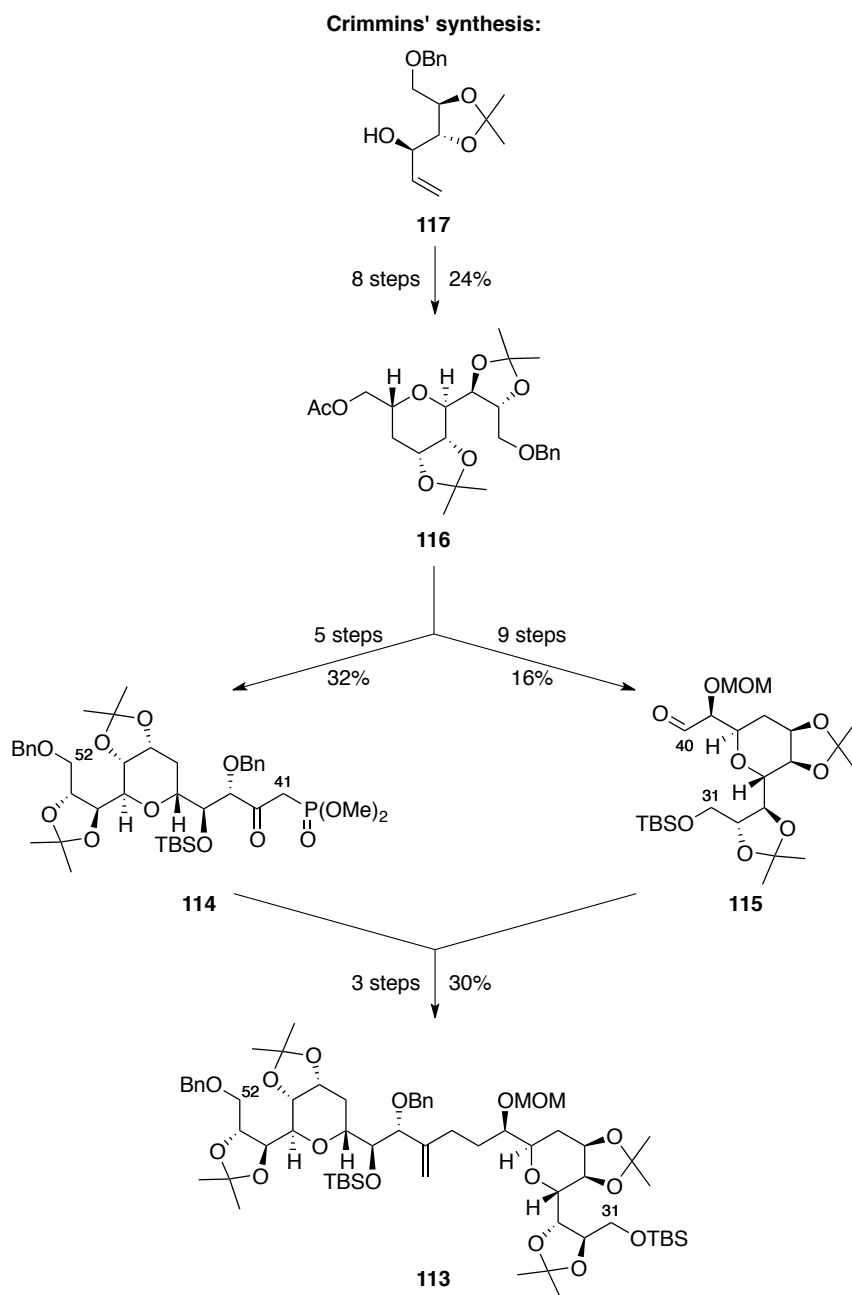
Scheme 5.8.1: Overview of Amphidinol 3 THP Segment Syntheses



Scheme 5.8.2: Overview of Amphidinol 3 THP Segment Syntheses (Cont.)



Scheme 5.8.3: Overview of Amphidinol 3 THP Segment Syntheses (Cont.)

Scheme 5.8.4: Overview of Amphidinol 3 THP Segment Syntheses (Cont.)

20 longest linear steps, 1.1% overall yield

5.9 References

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Chapter 6

Synthesis of the Common THP Fragment of Amphidinol 3

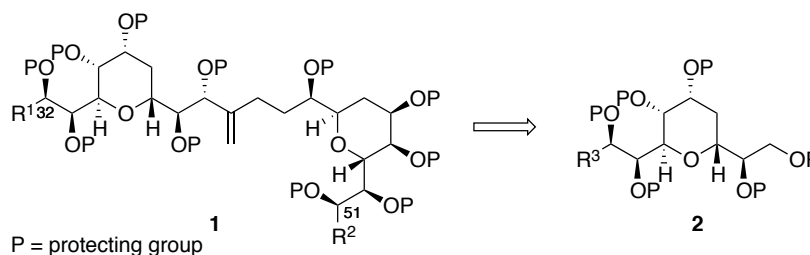
6.1 Introduction

In the following chapter, the development of a novel TST-based methodology for the stereoselective synthesis of *syn*- and *anti*-tetrahydropyrans (THPs) is discussed. This led to the realisation of an innovative strategy, which accounted for a highly stereoselective and efficient preparation of *syn*- and *anti*-tetrahydropyrans, present in numerous natural products. Furthermore, the application of this approach led to a convergent synthesis of a common THP fragment of amphidinol 3.

6.2 Analysis of the Common THP Fragment of Amphidinol 3

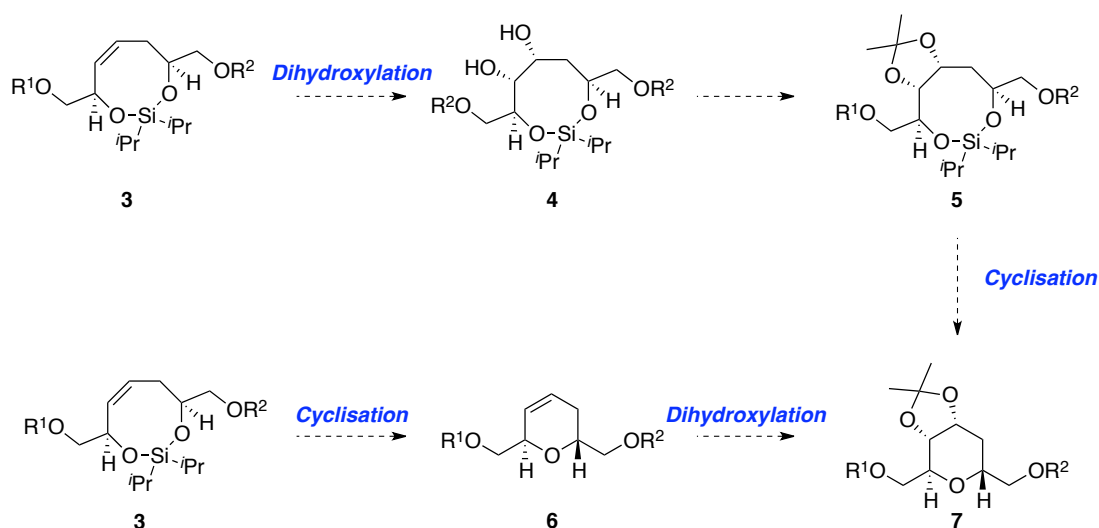
In the strategic planning for the synthesis of amphidinol 3 we aimed to develop a unified approach towards the natural product based on the application of the TST-based strategy outlined earlier. The evaluation of the *bis*-THP fragment of AM3 revealed the presence of two identical tetrahydropyran rings. Subsequently, the whole segment could be obtained with a high degree of convergence by the synthesis of the common THP intermediate **2**, as was the case with related approaches (Figure 6.2.1).

Scheme 6.2.1: Retrosynthetic Analysis of the *bis*-THP fragment of AM3



We hypothesised two avenues for the construction of the model *anti*-THP **7** (Scheme 6.2.2). Based on the knowledge acquired from the hydroboration reactions of the cyclic silaketals (Chapter 4), we envisaged that the dihydroxylation of *syn*-silaketal **3** would introduce the desired dioxygen functionality in a highly stereoselective manner, governed by the absolute configuration of the allylic stereocentre in **3**. Subsequent diol protection in **4** and functional group manipulations could provide the *anti*-THP unit **7**, which would constitute a model common fragment of the *bis*-THP segment of amphidinol 3.

Scheme 6.2.2: *Synthetic Hypothesis of the anti-THP 7 Formation*

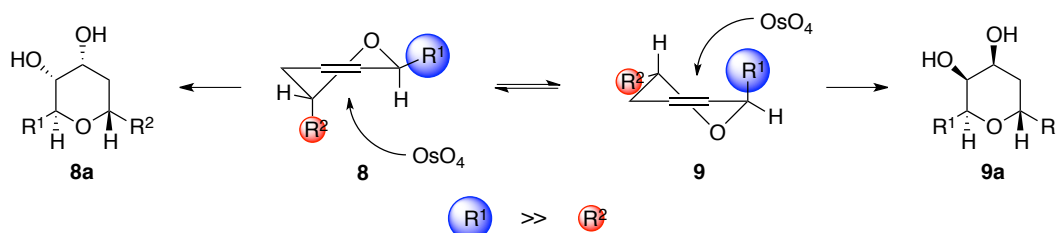


Furthermore, we also planned an alternative route to **7**. At the outset, deprotection of silaketal **3** would furnish the diol intermediate, which could be cyclised to dihydropyran **6** by exploiting the difference in the reactivity between the allylic and homoallylic alcohols. Ultimately, the stereoselective dihydroxylation and protection of the diol intermediate would deliver the common THP fragment **7**.

According to the previous studies on the dihydroxylation of *anti*-dihydropyrans (DHPs), in the synthesis of amphidinol 3¹ and other natural products,² an important conclusion regarding the stereochemical outcome of the dihydroxylation of **6** could be predicted. Since *anti*-DHP rings favour a twisted

conformation, consisting of two equilibrating conformers **8** and **9**, the stereoselective osmylation of the alkene represents a significant challenge due to the uneven shielding of olefin (Scheme 6.2.3). Thus, as a general strategy, increasing the steric bulk of R^1 and decreasing R^2 is commonly exploited to achieve the preference for conformer **8** over **9** and deliver the requisite diol **8a** with acceptable levels of stereocontrol. As was highlighted in Chapter 5, this approach produces a marginal selectivity in the catalytic dihydroxylation (*ds* up to 5:1) and good selectivity (*ds* = 9:1) in the stoichiometric variant of the osmylation. However, the introduction of chiral ligands was typically necessary in the former process, while the latter resulted in difficulties associated with the utilisation of large quantities of toxic osmium(VIII) oxide and complications in the hydrolysis of the osmate ester intermediate.

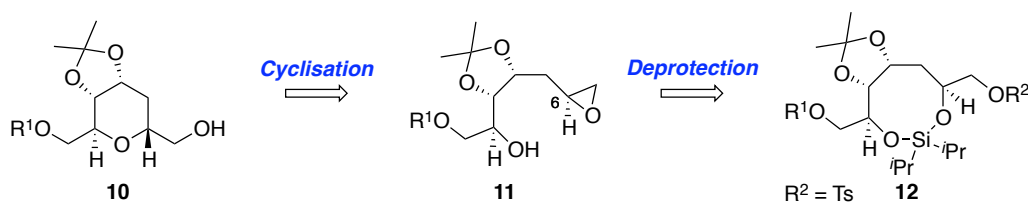
Scheme 6.2.3: *Conformational Equilibrium During the Dihydroxylation of anti-THP Rings*



While considering a synthetic strategy towards the common fragment of the *bis*-THP segment of AM3, we decided to exploit the first approach listed in Scheme 6.2.2 in the expectation that the assembly of **7** would be subject to substrate control, which could provide a more elegant route to the common THP fragment of AM3 and highlight the effectiveness of the TST-RCM-based methodology. Moreover, the application of dihydropyran dihydroxylation in conjunction with the cyclisation is well precedented, since these transformations have been utilised by other groups in the same context (*vide supra*).

Scheme 6.2.4 depicts the retrosynthetic analysis of the *anti*-THP fragment **10**. We hypothesised that the formation of the THP **10** could be achieved using a Lewis/Brønsted acid catalysed 6-*exo*-tet cyclisation of the δ -hydroxy epoxide **11** with complete regio- and stereoselectivity, and with inversion of the epoxide C6 stereocentre.³ The generation of the latter could be achieved *via* the fluoride-mediated desilylation of the tosylate **12**, which would proceed through an *intramolecular* cyclisation of the intermediate dihydroxytosylate.

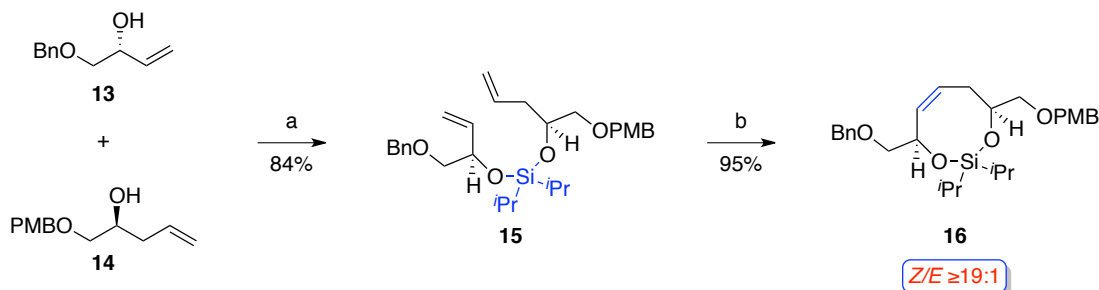
Scheme 6.2.4: Retrosynthetic Analysis of the *anti*-THP Unit **10**



6.3 Synthesis of the Model *anti*-THP Ring

The synthesis of the *anti*-THP fragment commenced from the formation of the mixed cyclic *syn*-silaketal **16** as outlined in Scheme 6.3.1. Generation of the ring-closing metathesis precursor **15** was accomplished using $i\text{Pr}_2\text{SiCl}_2$, as a temporary tether, and allylic **13** and homolallylic alcohol **14** in 84% yield.

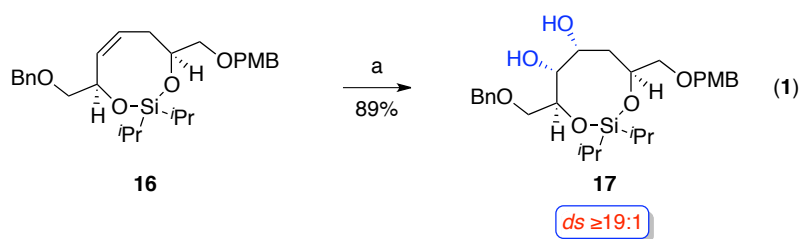
Scheme 6.3.1: Synthesis of the Cyclic *syn*-Silaketal **16**



Reaction conditions: a) **13**, $i\text{Pr}_2\text{SiCl}_2$, imid, DCM, 0 °C to RT, then **14**, imid, DCM, 0 °C to RT, 84%.
b) 1 mol% G-II, DCM, 40 °C, 95%, *Z/E* ≥ 19:1.

Treatment of the diene **15** with 1 mol% of Grubbs 2nd generation catalyst in DCM afforded the cyclic *anti*-silaketal **16** as a single geometrical isomer (*Z/E* \geq 19:1) in almost quantitative yield. It is noteworthy to mention that undesirable double bond migration was not detected during the process and the reaction was complete in less than 1 hour.

With the desired eight-membered cyclic alkene in hand, the pivotal dihydroxylation reaction was attempted. Gratifyingly, the catalytic osmylation under standard Upjohn conditions⁴ allowed for the stereoselective introduction of the diol in 89% yield and with excellent diastereoselectivity (*ds* \geq 19:1) by virtue of the cyclic stereocontrol offered by silaketal **16** (eq. 1).



Reaction conditions: a) *cat.* OsO₄, NMO, acetone/water (9:1), RT, 89%.

Notably, the competitive rearrangement of the diol *via* an intramolecular silyl migration was observed when the transformation was conducted at low concentration and over prolonged reaction times. However, this could be avoided by conducting the oxidation in a concentrated solution (*c* = 0.6 M), which only gave trace amounts of the migration products (*ds* \geq 10:1).

The stereochemical outcome of the transformation was explained using conformational analysis, as discussed in Chapter 4.⁵ The eight-membered *syn*-silaketal ring adopts the energetically preferable boat-boat conformation **18**, where the presence of the alkene and two oxygen atoms effectively minimise the transannular nonbonded interactions (Figure 6.3.1, benzyloxy groups are omitted for

clarity). The addition of the electrophile can only proceed from the less sterically hindered concave face of the molecule, since the benzyl group shields the alkene on the convex face. Furthermore, the Kishi model for the dihydroxylation of allylic alcohols could be successfully implemented to explain the selective formation of **17**.⁶ Arrangement of the eclipsed conformation **19** by the alkene **16** would direct the approaching osmium tetroxide to the face opposite to the silyloxy ether, due to the electrostatic repulsions between the electrophile and the oxygen lone pairs.

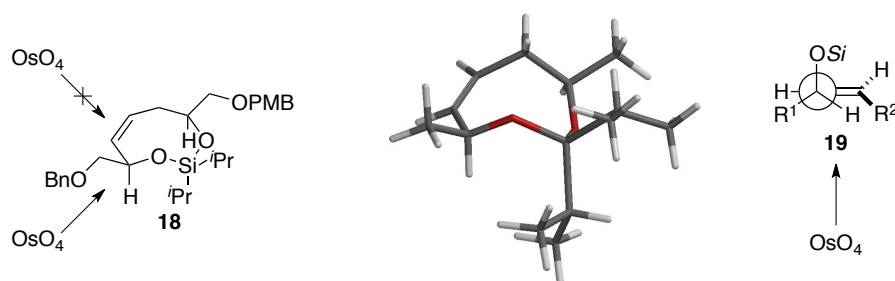


Figure 6.3.1: *Prediction of Stereochemistry of the Dihydroxylation Reaction of 16*

The relative stereochemistry of the diol was assigned using extensive 2D NOESY, COSY and coupling constant analysis (Figure 6.3.2).

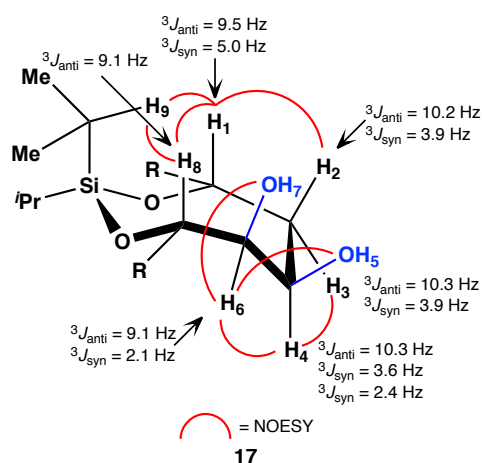


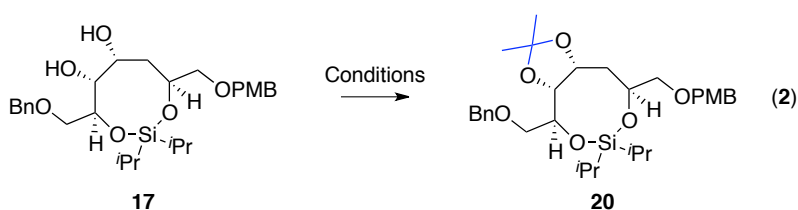
Figure 6.3.2: *Stereochemical Assignment of Diol 17*

Based on the data acquired, the molecule was predicted to adopt a boat-chair conformation, as supported by the strong nOe enhancements between the consecutive *syn*-hydrogens (H_1 - H_2 , H_3 - H_4 - H_6) and H_7 - H_6 - H_5 . Furthermore, the spatial arrangement of the silyldioxy group was established by the nOe signal between the *i*Pr group and two axial protons (H_9 - H_8 - H_1).

The coupling analysis provided additional evidence for the proposed relative stereochemistry. For example, typical 1,2-diaxial coupling constants were observed for the key protons including $J_{H1,H3}$ (9.9 Hz), $J_{H2,H4}$ (10.3 Hz) and $J_{H8,H6}$ (9.1 Hz) as well as 1,2-*syn* couplings $J_{H1,H2}$ (4.5 Hz), $J_{H3,H4}$ (3.8 Hz) and $J_{H4,H6}$ (2.3 Hz), pointing to the proposed boat-chair conformation adopted by diol **17**.

The next key step in the synthesis of the model common fragment of AM3 was the protection of diol **17**. Since we hypothesised a fluoride-mediated deprotection during the cyclisation, the 1,2-acetonide was elected as a masking group. Unfortunately the propensity of **17** to undergo an acid-catalysed rearrangement required a fine-tuning of the protection conditions (Table 6.3.1).

Table 6.3.1: Optimisation of Acetonide **20** Formation (eq. 2)



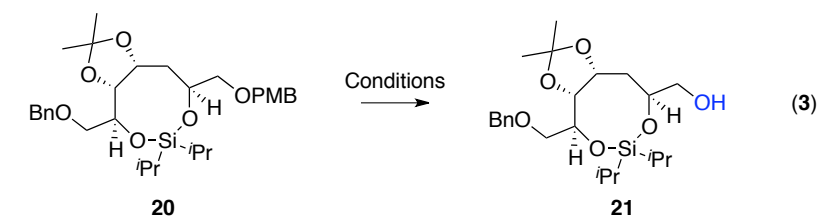
Entry	Conditions	Yield (%) ^a
1	<i>cat.</i> CSA, 2,2-DMP, DCM, RT	62
2	<i>cat.</i> PPTS, 2,2-DMP, DCM, RT	64
3	<i>cat.</i> PPTS, 2-methoxypropene, DCM, RT	75
4	<i>cat.</i> VO(OTf)₂, 2,2-DMP, MeCN, RT	91

^aIsolated yield.

Application of the standard conditions, namely catalytic CSA and 2,2-dimethoxypropane, gave the desired product **20** in average yield in conjunction with inseparable rearranged products (entry 1). We hypothesised that a more mildly acidic catalyst, *i.e.* PPTS, could be used to avoid the undesired silyl migration. To our dismay, this had little effect on the efficiency of the transformation (entry 2). Albeit the reactivity was improved by the use of the more reactive 2-methoxypropene electrophile (entry 3), the self-condensation of the latter during the protection made it difficult to isolate the pure product. Gratifyingly, the utilisation of VO(OTf)₂ mediated isopropylation conditions⁷ delivered the requisite acetonide **20** in high yield (91%). Notably, no silyl migration was observed under these conditions.

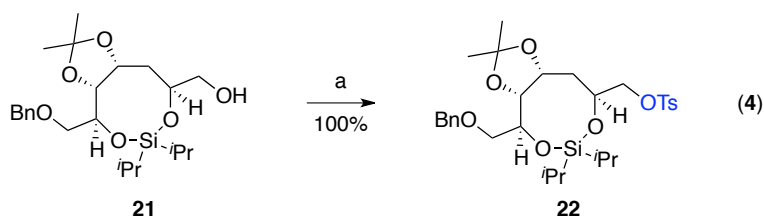
Encouraged by the success of the protection reaction, we initiated the examination of the chemoselective deprotection of the primary PMB ether and the ultimate conversion of the alcohol intermediate to tosylate **22**. Surprisingly, the cleavage of the *p*-methoxybenzyl ether in the presence of the primary benzyl group was troublesome (Table 6.3.2, eq. 3).

Table 6.3.2: Chemoselective Deprotection of the PMB ether **20** (eq. 3)



Entry	Conditions	Yield (%)
1	DDQ, DCM/pH 7 buffer, 0 °C	46
2	CAN, DCM, 0 °C	—
3	TMSI, DCM then K ₂ CO ₃ , 0 °C	51
4	<i>cat.</i> SnCl ₂ , TMSCl, anisole, DCM, −78 °C	67
5	SnCl₂, PhSH, DCM, −78 °C	81%

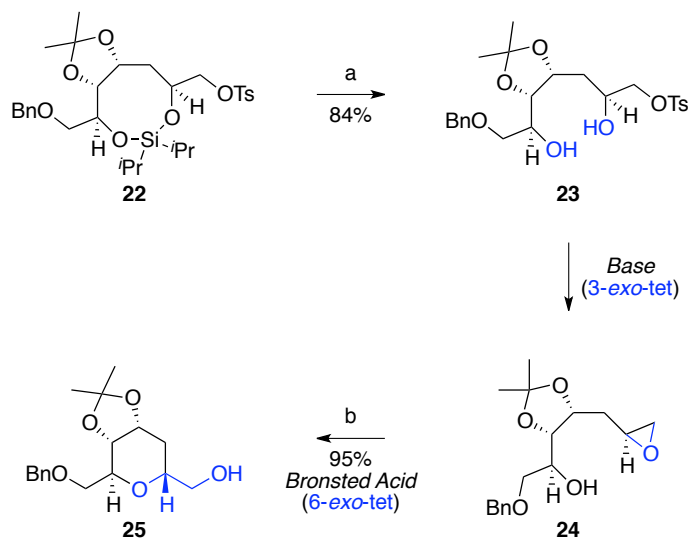
Standard conditions such as buffered DDQ, which were successfully employed in the synthesis of the polyol segment of AM3, led to the concomitant loss of the Bn ether and low yields of **21** (entry 1). Interestingly, ceric ammonium nitrate, which is known to be a selective reagent for PMB ether removal, was completely incompatible with this substrate and afforded only the desilylated product (entry 2). Selective conversion of PMBO group to TMS ether using TMSI/Et₃N and subsequent one-pot hydrolysis by K₂CO₃, reported by Kadota *et al.*,⁸ afforded only moderate yields of **21** (entry 3). The use of Lewis acid activation under mild conditions, as demonstrated by Akiyama and Ozaki, could effect selective removal of PMB group.⁹ Thus, a combination of catalytic SnCl₂, TMSCl and anisole improved the yield of **21** to 67%. Upon screening a range of conditions for the selective deprotection of **20**, it became apparent that the similar reactivity of both benzylic ethers could be attributed to the electronic impact of the silyloxy moiety in the α -position. We hypothesised that the utilisation of Lewis acid at low temperature could result in greater chemoselectivity and allow for a more efficient cleavage. Gratifyingly, we discovered that the application of stoichiometric SnCl₂ in conjunction with a thiophenol nucleophile at $-78\text{ }^{\circ}\text{C}$ ¹⁰ resulted in an instantaneous reaction and excellent selectivity favouring the monodeprotected product **21** (entry 5, 81% yield). With an efficient route to the primary alcohol **21** in hand, the formation of tosylate **22** was achieved in excellent yield using standard conditions (eq. 4).



Reaction conditions: a) TsCl, Et₃N, *cat.* DMAP, DCM, RT, 100%.

This success set the stage to test our proposed deprotection/double cyclisation transformation. Treatment of tosylate **22** with TBAF accounted for the cleavage of the silaketal and furnished **23** (Scheme 6.3.2). Subsequently, the basic reaction medium facilitated the *intramolecular* reaction of the intermediate dihydroxy tosylate **23** to afford the epoxy alcohol **24** through a 3-*exo*-tet cyclisation. Although a one-pot conversion to the **25** was viable at this stage simply by addition of the excess of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, the isolation of alcohol **25** in pure form proved to be challenging due to an impurity formed during the deprotection step. Therefore a two-step approach was pursued. Hence, in agreement with our hypothesis a Brønsted acid activation of the epoxide moiety in **24** promoted the critical *intramolecular* nucleophilic cyclisation to furnish the *anti*-THP ring **25** in excellent yield *via* a 6-*exo*-tet cyclisation, which represents a model *anti*-THP fragment of amphidinol 3.

Scheme 6.3.2: *Synthesis of the Model Common anti-THP Fragment of AM3*



Reaction conditions: a) TBAF, THF, 0 °C, 84%.
 b) *cat.* CSA, DCM, 0 °C, 85%

6.4 Retrosynthetic Analysis of the *syn*-THP Ring

The successful implementation of the TST-based strategy for the construction of the *anti*-THPs let us to anticipate that we should be able to adapt the methodology for the preparation of the polysubstituted *syn*-THP rings, which are prevalent in many important natural products (Figure 6.4.1).

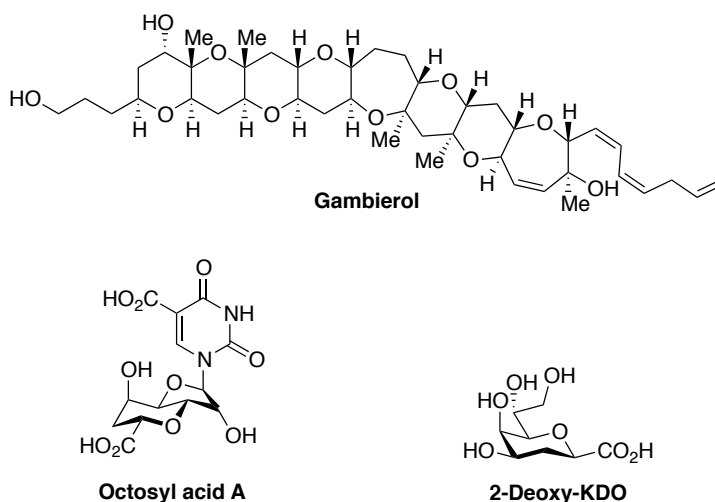
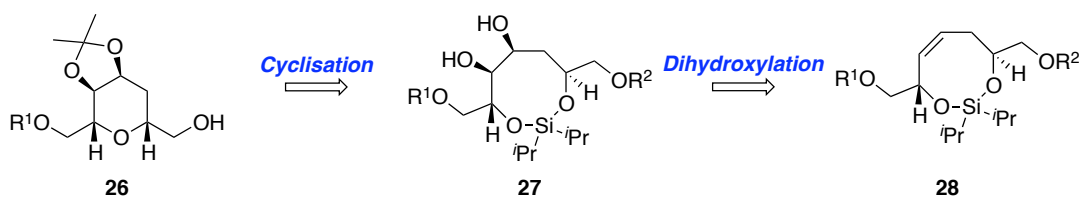


Figure 6.4.1: Selected Natural Products with the *syn*-THP Ring Functionality

We assumed that the *syn*-THP **26** could be obtained from diol **27** using the cyclisation reaction outlined in Chapter 6.3.2 (Scheme 6.4.1). Subsequently, the catalytic dihydroxylation of the cyclic *anti*-silaketal **28** was envisaged to deliver **27**, which would proceed from the less sterically encumbered face of the alkene, by analogy with the reaction of *syn*-silaketal **16**. Additionally, this transformation would be important test of the influence of the homoallylic stereocentre on the facial selectivity of the osmylation reaction.

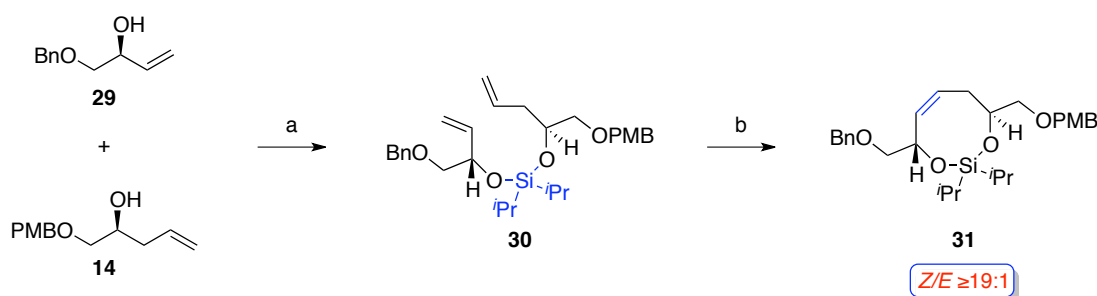
Scheme 6.4.1: Retrosynthetic Analysis of the *syn*-THP Ring Formation



6.5 Synthesis of the *syn*-THP Ring

The synthesis of the *syn*-THP unit was initiated with the formation of the desired mixed silaketal **31** in 82% yield from alcohols **30** and **14** (Scheme 6.5.1). Subsequent RCM of the diene using Grubbs 2nd generation catalyst afforded the cyclic *anti*-silaketal **31** with excellent *Z/E* control (98% yield).

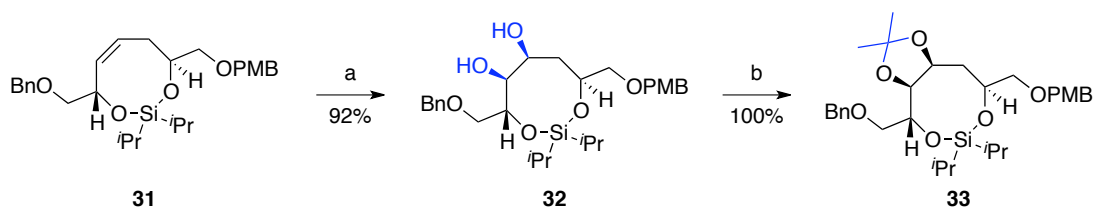
Scheme 6.5.1: *Synthesis of the Cyclic anti-Silaketal 31*



Reaction conditions: a) **29**, $i\text{Pr}_2\text{SiCl}_2$, imid, DCM, 0 °C to RT, then **14**, imid, DCM, 0 °C to RT, 82%. b) 1 mol% G-II, DCM, 40 °C, 98%, *Z/E* \geq 19:1.

Our next task was to extend the dihydroxylation methodology to the *anti*-silaketal **31**. Gratifyingly, the addition of catalytic OsO_4 in the presence of NMO in a mixture of acetone and water resulted in excellent 1,2-stereoselection from the resident allylic stereocentre and afforded the requisite diol **32** as a single diastereoisomer (Scheme 6.5.2).

Scheme 6.5.2: *Synthesis of Acetonide 33*



Reaction conditions: a) *cat.* OsO_4 , NMO, acetone/water (9:1), RT, 92%, *ds* \geq 19:1. b) *cat.* $\text{VO}(\text{OTf})_2$, 2,2-DMP, MeCN, RT, 100%.

It is noteworthy that rearrangement products were not observed in this instance, even after prolonged reaction times and with reduced catalyst loading, which could be attributed to the lower ring strain energy within the molecule when compared to **18**.

Analogous to the osmylation of *syn*-silaketals, the addition of the electrophile to **31** proceeded from the less sterically hindered face of the olefin residing in the boat-chair conformation **34** (Figure 6.5.1). The stereochemical outcome of the transformation was in agreement with Kishi's model **35**, predicting the attack of the OsO_4 progressing perpendicular to silyloxy functionality.

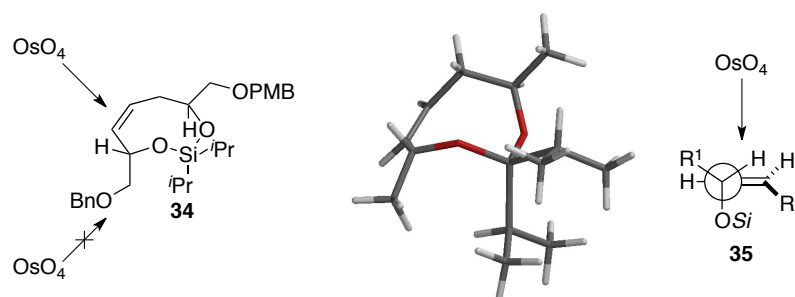


Figure 6.5.1: Prediction of Stereochemistry of the Dihydroxylation Reaction of **31**

The relative stereochemistry of the dihydroxylation product was deduced using the extensive 2D NOESY, COSY and coupling constant analysis (Figure 6.5.2). The spectroscopic data strongly suggested that diol **32** adopted a twisted boat-chair conformation,¹¹ as supported by strong nOe enhancements between the consecutive *syn*-hydrogens ($\text{H}_1\text{-H}_2$, $\text{H}_1\text{-H}_4\text{-H}_6$) and $\text{H}_3\text{-H}_8$, residing on the bottom face of the molecule. Additionally, nOe signals were evident between the two distinctive methyl groups and protons H_1 and H_8 . Analysis of coupling constants contributed to the proposed arrangement of **32**. The typical 1,2-diaxial coupling constants were observed for the protons including $J_{\text{H}_1,\text{H}_3}$ (10.5 Hz), $J_{\text{H}_3,\text{H}_4}$ (7.7 Hz) and $J_{\text{H}_6,\text{H}_8}$ (9.1 Hz) in addition to 1,2-*syn* couplings $J_{\text{H}_4,\text{H}_6}$ (2.0 Hz).

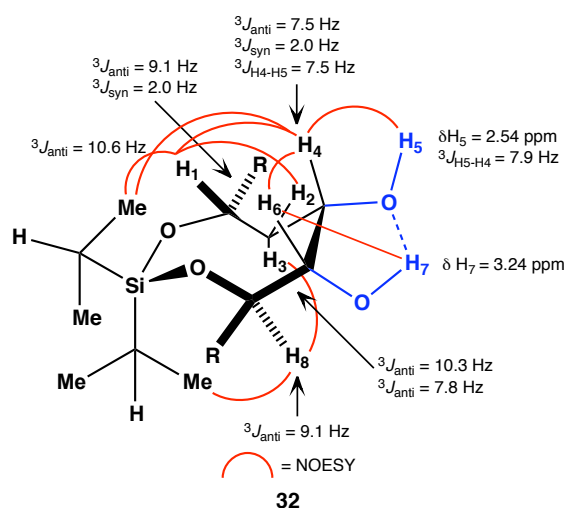
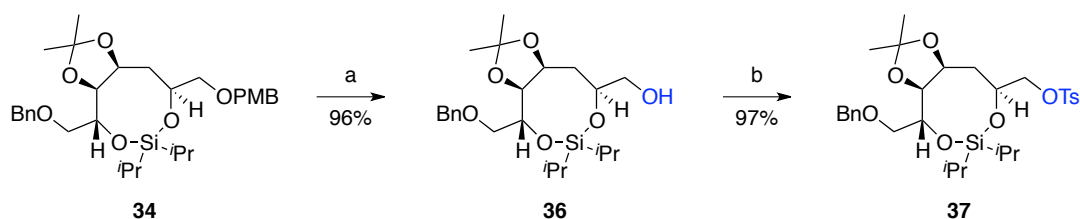


Figure 6.5.2: Stereochemical Assignment of Diol **32**

The conformational preference of diol **32** could be attributed to the stabilising effect of a hydrogen bond formed between OH₇ and OH₅, where H₇ is in the centre of the hydrogen bond network, which is consistent with its downfield shifted resonance at 3.24 ppm, while H₅ was observed at 2.54 ppm. Notably, hydroxyl protons are coplanar with H₄ and H₆, which was apparent from nOe experiments. It is worth mentioning that the conformational preference of **32** was fully supported by conformer searches using Spartan '08, calculated at a semi-empirical level of theory using an AM1 basis set.

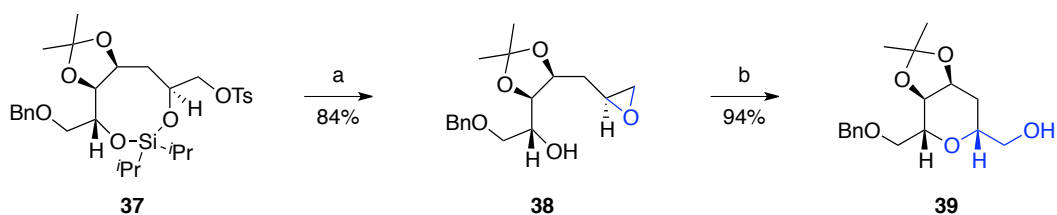
With the requisite diol **32** in hand, the formation of acetone **33** was then secured using previously optimised conditions, which involved the use of catalytic VO(OTf)₂ and 2,2-DMP, in excellent yield. Gratifyingly, the silyl migration products were not observed by ¹H NMR analysis.

The synthetic sequence leading to tosylate **37** is shown in Scheme 6.5.3. Chemoselective removal of the PMB ether **34** using SnCl₂/PhSH mixture, followed by tosylation of the intermediate alcohol **36** afforded the cyclisation precursor **37** in 93% yield over 2 steps.

Scheme 6.5.3: Synthesis of Tosylate 37

Reaction conditions: a) SnCl_2 , PhSH, DCM, -78°C , 96%. b) TsCl, Et_3N , *cat.* DMAP, DCM, RT, 97%.

Following the procedure described in Chapter 6.3, treatment of tosylate **37**, with TBAF afforded the hydroxyepoxide intermediate **38**, which was smoothly converted to the requisite *syn*-THP **39** via a pivotal 6-*exo*-tet cyclisation using catalytic CSA in 79% yield over 2 steps (Scheme 6.5.4).

Scheme 6.5.4: Synthesis of the *syn*-THP 39

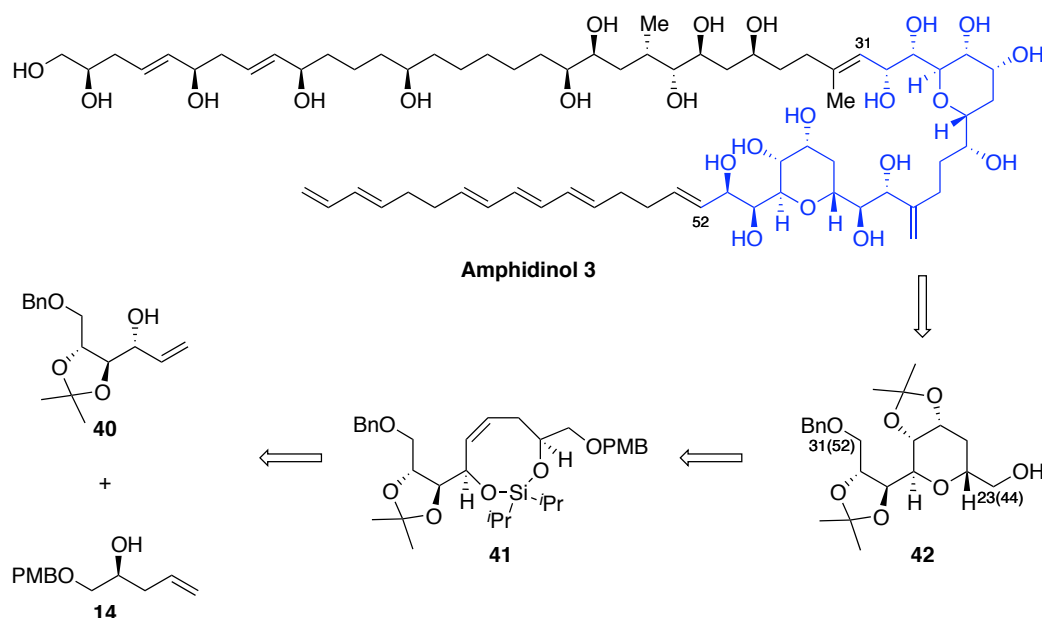
Reaction conditions: a) TBAF, THF, 0°C , 84%. b) *cat.* CSA, DCM, 0°C , 94%

In summary, a rapid and convergent synthesis of *syn*-THP and *anti*-THP rings was achieved by taking advantage of a novel and highly stereoselective TST-RCM/dihydroxylation methodology using the inherent substrate control. This sequence readily afforded the densely substituted tetrahydropyrans, relevant to a plethora of natural products, in just 8 longest linear steps starting from known materials and will likely find application in the field of the target-oriented synthesis.

6.6 Retrosynthetic Analysis of the Common THP Fragment of Amphidinol 3

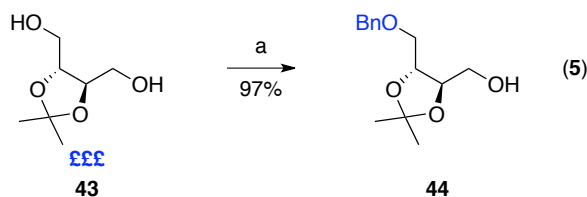
Having developed a stereoselective synthesis of the model *anti*-THP fragment of amphidinol 3, we turned our attention to the foremost goal, *i.e.* the synthesis of the advanced common THP fragment of the natural product. From a retrosynthetic perspective the route to **42** would require formation of the cyclic *syn*-silaketal **41**, hinged upon the TST formation between **14** and advanced allylic alcohol **40** with subsequent ring-closing metathesis (Scheme 6.6.1).

Scheme 6.6.1: Retrosynthetic Analysis of the bis-THP Fragment of Amphidinol 3



6.7 Synthesis of the Common THP Fragment of Amphidinol 3

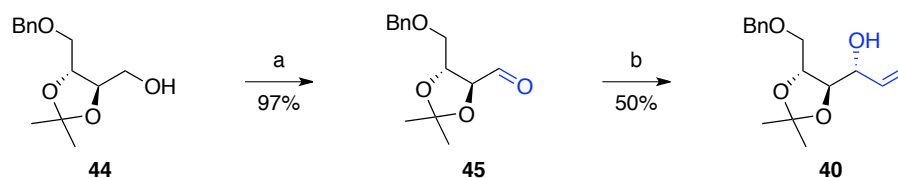
Synthesis of the allylic TST coupling fragment **40** was initiated by the monobenylation of the commercially available diol **43**. We were pleased to find that conditions, developed by Sauve for the monoprotection of symmetrical diols,¹² which involved the utilisation of Ag₂O as a base, afforded **44** on large scale in 70% yield 90% b.r.s.m., eq. 5), with easy recovery of the unreacted starting material and a trace of the dibenylation product.



Reaction conditions: a) BnBr , Ag_2O , DCM , RT , 70% (90% b.r.s.m.).

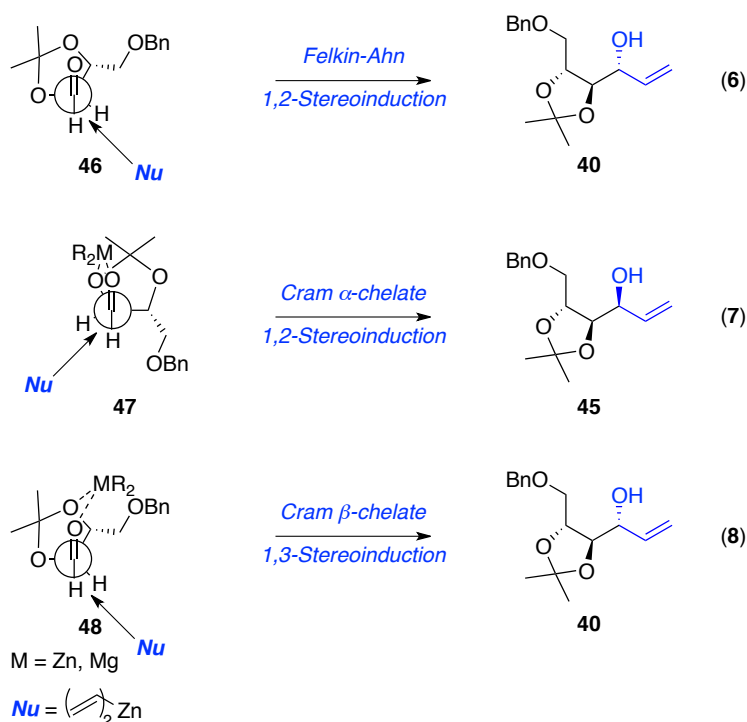
A Felkin-Ahn controlled vinyl organometallic addition to the alkoxy aldehyde **45** was anticipated to provide the allylic alcohol **40**. Following the precedent of Crimmins,¹³ divinyl zinc formation from the vinyl magnesium bromide and ZnCl_2 , succeeded by the addition of the former to aldehyde **45**, obtained *via* Swern oxidation of **44**,¹⁴ furnished the requisite alcohol **40** in modest yield (Scheme 6.7.1). Unfortunately, the stereoselectivity of the transformation was considerably lower than that reported (4:1 vs. 9:1). Subsequent attempts to optimise the reaction by employing various zinc salts, solvents and temperatures did not provide suitable conditions for the preparation of **40** in a satisfactory manner.

Scheme 6.7.1: Initial Approach to the Allylic Alcohol 40

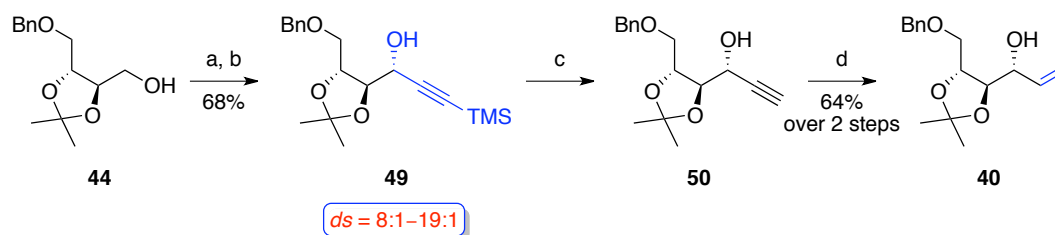


Reaction conditions: a) $(\text{COCl})_2$, DMSO , DIPEA , DCM , -78°C to RT . b) VinylMgBr , ZnCl_2 , $\text{PhMe/Et}_2\text{O}$, -78°C to RT , 50% over 2 steps.

Although Mukaiyama *et al.* explained the *anti*-selective addition to **45** by the Felkin-Ahn model **46** (eq. 6),^{15,16} in principle, the generation of mixed chelated species **47** and **48** could have a dramatic effect on the stereochemical outcome. Thus, formation of the Cram β -chelate **48** (eq. 8) would furnish the requisite alcohol **40**, whereas the α -chelate model **47** (eq. 7) could reverse the stereochemical sense of the addition and result in the accumulation of the undesired *syn*-adduct **45**.



In search of alternative routes to alcohol **40**, we were intrigued by the prospect of a highly stereoselective lithium trimethylsilylacetylide addition to the α,β -alkoxy aldehyde **45** in the presence of $\text{Ti}(\text{O}^i\text{Pr})_4$ and TiCl_4 (Scheme 6.7.2).^{14,15} Generation of the titanium acetylide species, followed by the addition of aldehyde **45** resulted in the propargylic alcohol **49** in 68% yield over 2 steps and with excellent stereocontrol ($ds \geq 19:1$). Notably, consistently high selectivity was obtained when reaction was performed on gram-scale. However, on larger scale (10-15 g) erosion in selectivity was observed ($ds = 8:1$). Although the diastereoisomers of **49** were inseparable at this stage, further synthesis of the mixed silaketal **51** accounted for their efficient separation.

Scheme 6.7.2: Alternative Approach to Alcohol 40

Reaction conditions: a) $(\text{COCl})_2$, DMSO, DIPEA, DCM, $-78\text{ }^\circ\text{C}$ to RT. b) HCCTMS, $^n\text{BuLi}$, $\text{Ti}(\text{O}^i\text{Pr})_4$, TiCl_4 , THF, $-78\text{ }^\circ\text{C}$ to RT, 68% over 2 steps, $ds = 19:1$ to $8:1$. c) TBAF, THF, RT, 97%. d) Red-Al, THF, reflux, 64% over 2 steps.

The stereochemical outcome of the transformation could be explained by the generation of the highly sterically demanding titanium nucleophile, which, by the virtue of coordinative saturation, could avoid the formation of chelated species (*vide supra*) and would direct the acetylide addition to aldehyde **45** in a Felkin-Ahn fashion (Figure 6.7.1).

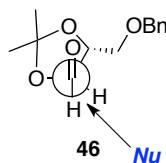


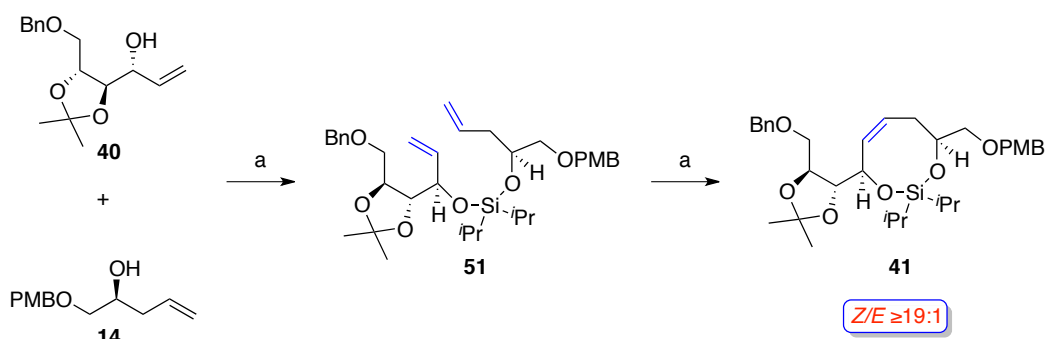
Figure 6.7.1: Felkin-Ahn Model for Acetylide Addition to 45

With an efficient route to **49** in hand we turned our attention to the construction of the allylic alcohol **40**. Thus, generation of alkyne **50** using TBAF in THF, followed by the hydroxyl-directed alkyne reduction to the alkene forged **40** in 64% yield over 2 steps. It should be noted that the reaction with soluble Red-Al was more beneficial than the commonly employed LiAlH_4 , since the transformation with the latter failed to go to completion due to the formation of the insoluble metal alkoxide intermediates.

With the required alcohol precursor in hand, we then followed the optimised strategy towards the THP ring as discussed in Chapter 6.3. Formation of the mixed

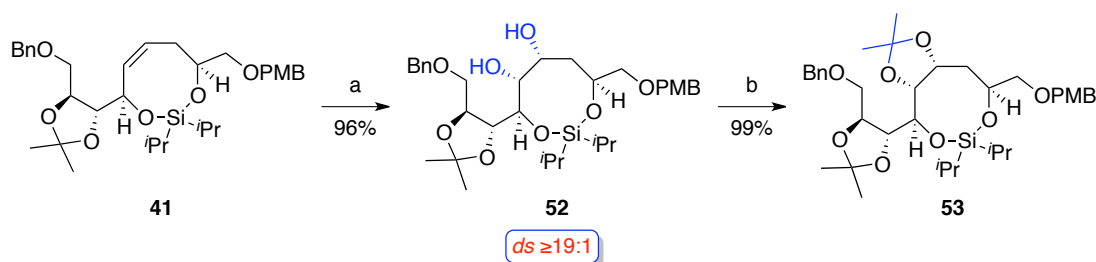
silaketal from **40** and **14** using $i\text{Pr}_2\text{SiCl}_2$ afforded smoothly **51** in 84% yield on up to 7 mmol scale (Scheme 6.7.3). The diene **51** was then taken forward to the TST-RCM reaction. Gratifyingly, introduction of the more sterically hindered 1,2-acetonide functionality on the left hand side of the molecule did not have an impact on the reaction efficiency and the requisite *syn*-silaketal **41** was obtained in excellent yield as a single (*Z*)-geometrical isomer by employing Grubbs 2nd generation catalyst in DCM.

Scheme 6.7.3: Formation of the Advanced *syn*-Silaketal **41**



Reaction conditions: a) **14**, $i\text{Pr}_2\text{SiCl}_2$, imid, DCM, 0 °C to RT, then **40**, imid, DCM, 0 °C to RT, 84%. b) 1 mol% G-II, DCM, 40 °C, 99%, *Z/E* $\geq 19:1$.

By analogy with model studies (*vide supra*), catalytic Upjohn dihydroxylation (*ds* $\geq 19:1$) and $\text{VO}(\text{OTf})_2$ mediated protection of the diol intermediate **52** furnished acetonide **53** in excellent overall yield (Scheme 6.7.4). Although some silyl migration was observed in the former step (*ds* $\geq 10:1$), careful flash chromatography accounted for the isolation of pure **52**.

Scheme 6.7.4: Formation of Acetonide **53**

Reaction conditions: a) *cat.* OsO₄, NMO, acetone/water (9:1), RT, $ds \geq 19:1$, 96%. b) *cat.* VO(OTf)₂, 2,2-DMP, MeCN, RT, 99%.

The stereochemistry of the dihydroxylation product **52** was assigned in a similar fashion to the diol **17** (*vide supra*).

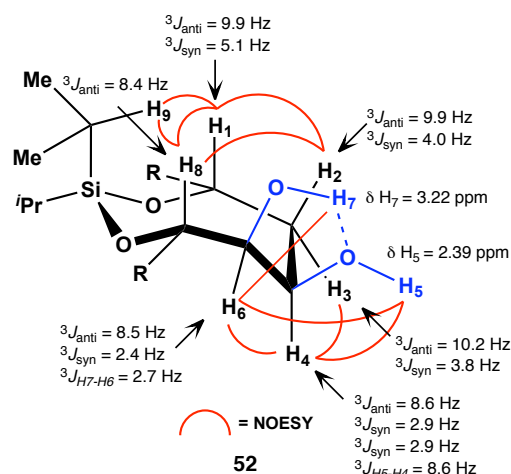


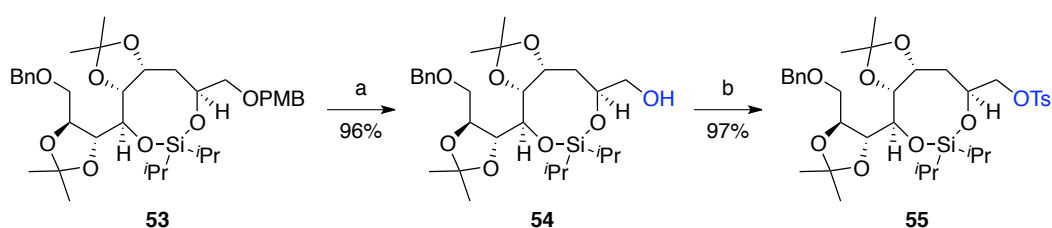
Figure 6.7.2: Stereochemical Assignment of Diol **52**

Examination of the spectroscopic data of diol **52** confirmed its stereochemical correlation with the model dihydroxylation product **17** (Figure 6.7.2). Specifically, the boat-chair conformation was consistent with nOe correlations between the *i*Pr group and pseudo-axial hydrogens (H₁-H₉-H₈), in addition to enhancements of *syn*-hydrogens (H₁-H₂-H₈). Furthermore, the presence of a nOe signal between H₃-H₄-H₆, residing on the bottom face of the molecule, and H₇-H₆-H₅-H₄, arising from the hydrogen bond network, contributed to the proposed spatial arrangement of the diol.

The suggested relative stereochemistry was consistent with the patterns of ^1H - ^1H coupling. Thus, typical 1,2-diaxial coupling constants were observed for a number of protons including $J_{\text{H1,H3}}$ (10.1 Hz), $J_{\text{H2,H4}}$ (9.3 Hz) and $J_{\text{H8,H6}}$ (8.5 Hz) as well as 1,2-*syn*-couplings $J_{\text{H1,H2}}$ (4.6 Hz), $J_{\text{H3,H4}}$ (3.4 Hz) and $J_{\text{H4,H6}}$ (2.7 Hz), further indicating that diol **53** adopted a boat-chair conformation.

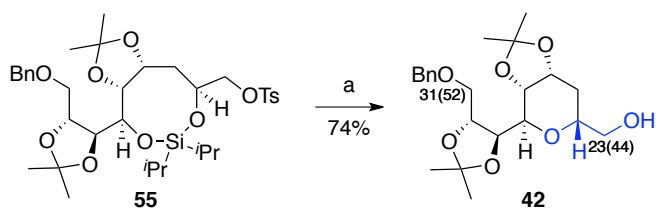
With the advanced acetonide **53**, containing the correct stereochemistry, we moved forward towards the synthesis of tosylate **55** and formation of the common THP fragment of amphidinol 3. Chemoselective deprotection of the primary benzyl ether in **53** using $\text{SnCl}_2/\text{PhSH}$ at $-78\text{ }^\circ\text{C}$ and generation of the primary tosylate **55** afforded the requisite cyclisation precursor in 93% yield over 2 steps (Scheme 6.7.5).

Scheme 6.7.5: Formation of Tosylate 55



Reaction conditions: a) SnCl_2 , PhSH , DCM , $-78\text{ }^\circ\text{C}$, 96%. b) TsCl , Et_3N , *cat.* DMAP , DCM , RT , 97%.

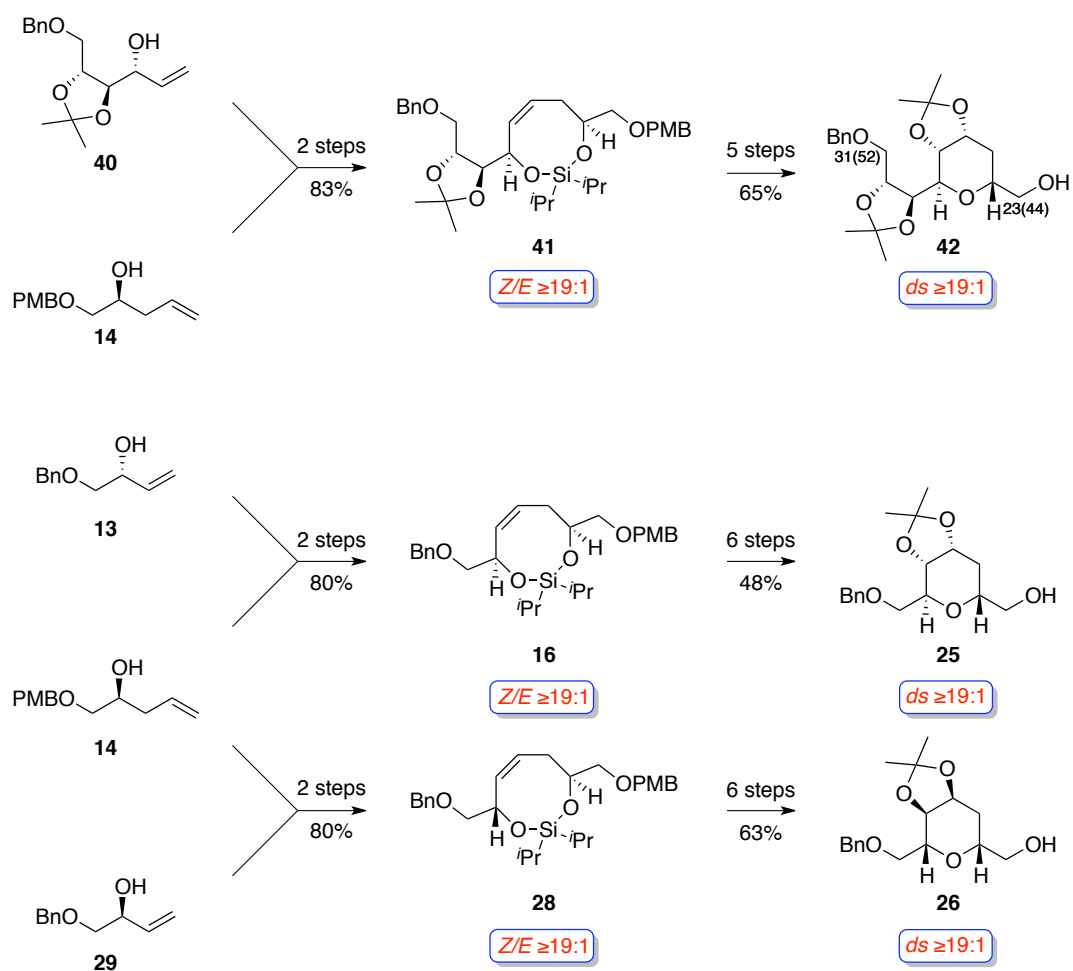
At this stage, we elected to exploit a one-pot cyclisation strategy to effect the formation of the common THP fragment of amphidinol 3 from tosylate **55** (Scheme 6.7.6). Thus, treatment of **55** with TBAF afforded the hydroxy epoxide intermediate, which was not isolated and converted to alcohol **42** upon addition of the excess of Lewis acid in 74% yield. Notably, the latter product constitutes the C31(52)-C39(44) THP fragment of amphidinol 3.

Scheme 6.7.6: Formation of the Common THP Fragment **42**

Reaction conditions: a) TBAF, then BF₃·Et₂O, THF, 0 °C, 74%.

6.8 Conclusion

In summary, a substrate-controlled synthesis of the common C31(52)-C39(44) THP fragment of amphidinol 3 was achieved *via* the development of a novel TST-RCM/dihydroxylation methodology in conjunction with a pivotal 6-*exo*-trig cyclisation of a hydroxy epoxide in 7 longest linear steps from known materials and exceptional 58% overall yield. The succinct route to the fragment could be utilised in further studies directed towards a highly convergent bidirectional approach towards the *bis*-THP unit of the natural product. In addition, the methodology allowed for an expeditious stereoselective formation of the challenging tetrasubstituted *syn*- and *anti*-THP rings starting from the readily available allylic and homoallylic alcohols. In principle this transformation could be extended towards the formation of fully substituted THP rings present in numerous natural products and the preparation of the novel sugars.

Scheme 6.8.1: Overview of Syntheses of THP Rings Using TST-RCM

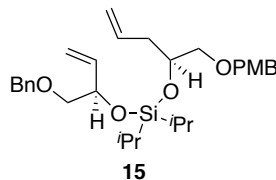
6.9 Experimental

6.9.1 General Information

All reactions were carried out under Argon atmosphere, unless otherwise stated. Anhydrous DCM, hexane, Et₂O were obtained by passing degassed solvents through activated alumina columns in a Grubbs solvent purification system (*PureSolv MD-6* of *Innovative Technology Inc.*). Anhydrous THF was obtained by distillation from benzophenone ketyl. Anhydrous MeCN was purchased from *Aldrich*. Et₃N, DIPEA, BF₃·Et₂O were distilled from CaH₂ under nitrogen and stored under 4 Å MS. For other general information, see Chapter 2.

6.9.2 Experimental Procedures

General procedure for the temporary silicon tether formation.



(4*S*,8*R*)-4-Allyl-6,6-diisopropyl-1-(4-methoxyphenyl)-11-phenyl-8-vinyl-2,5,7,10-tetraoxa-6-silaundecane (15)

The procedure requires usage of Schlenk techniques and performed under an atmosphere of argon at all operational steps! The 250 mL round bottom Schlenk flask was charged with dry imidazole (1.123 g, 16.50 mmol) and dissolved in DCM (77 mL). The solution was cooled to 0 °C and *i*Pr₂SiCl₂ (2.71 mL, 15.00 mmol) was added dropwise. After *ca.* 10 min a solution of **13** (0.891 g, 5.0 mmol) in DCM (3 mL) was added using a syringe pump over *ca.* 5 h and the reaction left to warm to room temperature. After *ca.* 13 h (TLC control) the reaction mixture was

concentrated under reduced pressure using a dry ice trap. The residue was triturated with hexane (24 mL) and the solution was carefully decanted from precipitates using a syringe into a separate 250 mL Kugelrohr flask (3x). The hexane washings were concentrated under reduced pressure using a dry ice trap and the residue was heated at 75 °C *in vacuo* (1 Torr) for *ca.* 3 h to remove the excess of $i\text{Pr}_2\text{SiCl}_2$. The crude monochloroalkoxysilane (~5 mmol) was cooled to 0 °C and imidazole (1.021 g, 15.00 mmol) in DCM (8 mL with washings) was added, followed by a **14** (1.778 g, 8.00 mmol) in DCM (12 mL with washings) and the reaction was warmed to room temperature. After 15 h (TLC control) the reaction mixture was quenched with saturated aqueous NH_4Cl and partitioned between Et_2O and water. Phases were separated and the aqueous layer was washed with Et_2O (2x). The combined organic layers were washed with water (2x), brine, dried (MgSO_4), filtered and concentrated. Purification by flash chromatography (silica gel, Et_2O /hexanes – 1:16) afforded the mixed silaketal **15** (2.14 g, 4.18 mmol, 84% yield) as a colourless oil.

$R_f = 0.26$ (Et_2O /hexanes – 1:20).

$[\alpha]_D^{20} +14.8$ (c 1.0, CHCl_3).

^1H NMR (500 MHz, C_6D_6) δ 7.36-7.26 (m, 2H), 7.22-7.19 (m, 2H), 7.17-7.15 (m, 2H), 7.09-7.06 (m, 1H), 6.79-6.76 (m, 2H), 5.97 (ddt, $J = 17.2, 10.1, 7.1$ Hz, 1H), 5.91 (ddd, $J = 17.2, 10.5, 5.5$ Hz, 1H), 5.36 (dt, $J = 17.2, 1.7$ Hz, 1H), 5.10 (ddt, $J = 17.2, 12.3, 1.2$ Hz, 1H), 5.06 (dt, $J = 10.5, 1.7$ Hz, 1H), 5.05 (ddt, $J = 10.2, 2.2, 1.1$ Hz, 1H), 4.67 (app. ddt, $J = 11.9, 5.7, 1.3$ Hz, 1H), 4.36-4.32 (m, 2H), 4.33 (s, 2H), 4.29 (app. dt, $J = 11.1, 5.5$ Hz, 1H), 3.50 (dd, A of ABX, $J_{AB} = 9.4$ Hz, $J_{AX} = 1.5$ Hz, 1H), 3.48 (dd, A of ABX, $J_{AB} = 9.5$ Hz, $J_{AX} = 0.5$ Hz, 1H), 3.42 (dd, B of ABX, $J_{AB} = 9.4$ Hz, $J_{BX} = 5.5$ Hz, 1H), 3.35 (dd, B of ABX, $J_{AB} = 9.4$ Hz, $J_{BX} = 5.3$ Hz, 1H), 3.30 (s, 3H), 2.50 (app. dddt, A of ABXYZ₂, $J_{AB} = 12.7$ Hz, $J_{AX} = 8.2$ Hz, $J_{AY} = 5.7$ Hz,

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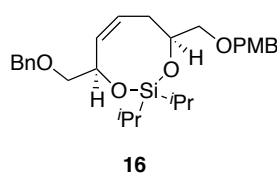
$J_{AZ} = 1.2$ Hz, 1H), 2.43 (app. dddt, B of ABXYZ₂, $J_{AB} = 12.9$ Hz, $J_{BX} = 7.5$ Hz, $J_{BY} = 5.4$ Hz, $J_{BZ} = 1.2$ Hz, 1H), 1.21-1.04 (m, 5H), 1.18 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H).

¹³C NMR (125 MHz, C₆D₆) δ 159.75 (e), 139.23 (o), 139.01 (e), 135.15 (o), 131.08 (e), 129.51 (o), 128.55 (o), 127.89 (o), 127.71 (o), 117.25 (e), 115.11 (e), 114.06 (o), 75.53 (e), 73.96 (e), 73.47 (e), 73.20 (e), 72.84 (o), 71.33 (o), 54.79 (o), 39.76 (e), 17.86 (o), 17.83 (o), 13.37 (o), 13.23 (o).

IR (Neat) 2943 (m), 2864 (s), 1641 (w), 1613 (w), 1587 (m), 1090 (vs), 1037 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₃₀H₄₄O₅NaSi 535.2856, found 535.2859.

General procedure for the temporary silicon-tethered ring-closing metathesis.



(4*S*,8*R*,*Z*)-8-((Benzyloxy)methyl)-2,2-diisopropyl-4-(((4-methoxybenzyl)oxy)methyl)-5,8-dihydro-4*H*-1,3,2-dioxasilocine (16)

To a solution of diene **15** (0.977 g, 1.91 mmol) in DCM (185 mL) was added Grubbs 2nd generation catalyst (0.0162 g, 0.019 mmol) as solution in DCM (5 mL with washings). The reaction mixture was refluxed for *ca.* 1 h (TLC control), before it was cooled to room temperature and treated with DMSO (6.8 mL, 95 mmol). After *ca.* 16 h the reaction was concentrated *in vacuo* and passed through a pad of silica gel (washed with Et₂O/petroleum ether – 1:5). Purification by flash chromatography (Et₂O/hexanes – 1:12, 1:10) afforded alkene **16** (0.881 g, 1.82 mmol, 95% yield) as a colourless oil.

R_f = 0.63 (Et₂O/hexanes – 1:1).

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$[\alpha]_{\text{D}}^{20} -1.3$ (c 1.0, CHCl_3).

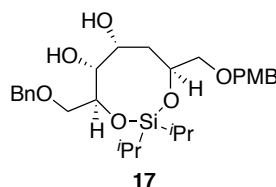
^1H NMR (500 MHz, C_6D_6) δ 7.32-7.30 (m, 2H), 7.20-7.16 (m, 4H), 7.11-7.08 (m, 1H), 6.80-6.77 (m, 2H), 5.79 (dd, A of ABX, A of ABX, $J_{AB} = 11.0$ Hz, $J_{AX} = 6.3$ Hz, 1H), 5.63 (q, $J = 9.4$ Hz, 1H), 4.70 (q, $J = 5.9$ Hz, 1H), 4.40 (d, A of AB, $J_{AB} = 12.4$ Hz, 1H), 4.41 (d, B of AB, $J_{AB} = 12.4$ Hz, 1H), 4.33 (d, A of AB, $J_{AB} = 11.7$ Hz, 1H), 4.31 (d, B of AB, $J_{AB} = 11.7$ Hz, 1H), 4.29 (app. dtd, $J = 7.5, 5.6, 3.7$ Hz, 1H), 3.54 (dd, A of ABX, $J_{AB} = 9.7$ Hz, $J_{AX} = 6.4$ Hz, 1H), 3.50 (dd, A of ABX, $J_{AB} = 9.1$ Hz, $J_{AX} = 5.3$ Hz, 1H), 3.44 (dd, B of ABX, $J_{AB} = 9.7$ Hz, $J_{BX} = 5.1$ Hz, 1H), 3.54 (dd, B of ABX, $J_{AB} = 9.0$ Hz, $J_{BX} = 7.7$ Hz, 1H), 3.31 (s, 3H), 2.62 (ddd, A of ABXY, $J_{AB} = 13.8$ Hz, $J_{AX} = 7.6$ Hz, $J_{AY} = 6.2$ Hz, 1H), 2.43 (ddd, B of ABXY, $J_{AB} = 13.5$ Hz, $J_{BX} = 9.5$ Hz, $J_{BY} = 3.8$ Hz, 1H), 1.25-1.09 (m, 1H), 1.19 (d, $J = 1.4$ Hz, 3H), 1.17 (d, $J = 1.4$ Hz, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.02 (sextet, $J = 7.4$ Hz, 1H).

^{13}C NMR (125 MHz, C_6D_6) δ 159.76 (e), 139.30 (e), 134.32 (o), 131.00 (e), 129.46 (o), 129.32 (o), 128.55 (o), 127.66 (o), 127.63 (o), 114.10 (o), 74.87 (e), 73.51 (e), 73.42 (e), 73.17 (o), 73.11 (e), 69.30 (o), 54.79 (o), 32.83 (e), 17.98 (o), 17.94 (o), 17.88 (o), 17.86 (o), 13.61 (o), 13.45 (o).

IR (Neat) 2942 (m), 2864 (m), 1612 (w), 1586 (w), 1085 (vs), 1036 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{28}\text{H}_{40}\text{O}_5\text{NaSi}$ 507.2543, found 507.2540.

General procedure for the dihydroxylation of cyclic silaketals.



(4*S*,5*R*,6*R*,8*S*)-4-((Benzyloxy)methyl)-2,2-diisopropyl-8-(((4-methoxybenzyl)oxy)methyl)-1,3,2-dioxasilocane-5,6-diol (17)

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A solution of **16** (0.1683 g, 0.347 mmol), NMO (0.122 g, 1.042 mmol) in a 10:1 mixture of acetone and water (0.605 mL) was treated with osmium(VIII) oxide (0.110 mL, 4% in water, 0.017 mmol) and stirred for *ca.* 2 h (TLC control). The reaction mixture was quenched with saturated aqueous Na₂SO₃ and partitioned between EtOAc and water. Phases were separated and the aqueous layer was washed with EtOAc (2x). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et₂O/hexanes – 1:1, 2:1, 3:1, 20:1) afforded diol **17** (0.160 g, 0.308 mmol, 89% yield) as a colourless oil.

R_f = 0.07 (Et₂O/hexanes – 1:1).

$[\alpha]_{\text{D}}^{20} +7.6$ (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.37-7.28 (m, 5H), 7.27-7.25 (m, 2H), 6.91-6.86 (m, 2H), 4.60 (d, A of AB, J_{AB} = 12.0 Hz, 1H), 4.57 (d, B of AB, J_{AB} = 11.9 Hz, 1H), 4.49 (s, 2H), 4.34 (app. dq, J = 9.9, 5.0 Hz, 1H), 4.26 (ddd, J = 10.3, 3.6, 2.4 Hz, 1H), 4.10 (app. dt, A of ABX₂, J_{AB} = 9.1 Hz, J_{AX} = 5.4 Hz, 1H), 3.96 (dd, B of ABX, J_{AB} = 9.1 Hz, J_{BX} = 2.1 Hz, 1H), 3.80 (s, 3H), 3.70 (dd, A of ABX, J_{AB} = 9.5 Hz, J_{AX} = 4.9 Hz, 1H), 3.60 (dd, B of ABX, J_{AB} = 9.6 Hz, J_{BX} = 5.8 Hz, 1H), 3.46 (dd, A of ABX, J_{AB} = 9.8 Hz, J_{AX} = 5.8 Hz, 1H), 3.38 (dd, B of ABX, J_{AB} = 9.8 Hz, J_{BX} = 5.0 Hz, 1H), 3.31 (br s, 1H), 2.52 (br s, 1H), 2.13 (ddd, A of ABXY, J_{AB} = 14.0 Hz, J_{AX} = 10.2 Hz, J_{AY} = 3.9 Hz, 1H), 1.75 (ddd, B of ABXY, J_{AB} = 13.9 Hz, J_{BX} = 10.3 Hz, J_{BY} = 3.7 Hz, 1H), 1.17 (septet, J = 7.3 Hz, 1H), 1.07 (d, J = 7.6 Hz, 3H), 1.05 (d, J = 7.7 Hz, 3H), 1.04 (d, J = 6.7 Hz, 3H), 1.03 (d, J = 7.2 Hz, 3H), 1.01-0.94 (m, 1H).

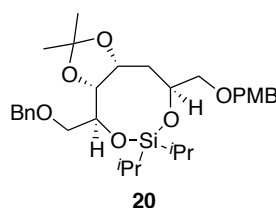
¹³C NMR (125 MHz, CDCl₃) δ 159.20 (e), 137.82 (e), 130.49 (e), 129.27 (o), 128.54 (o), 127.89 (o), 127.75 (o), 113.81 (o), 76.91 (o), 75.17 (e), 74.80 (e), 73.74 (e),

73.05 (e), 71.85 (o), 68.36 (o), 68.22 (o), 55.32 (o), 35.75 (e), 17.57 (o), 17.50 (o), 17.32 (o), 17.30 (o), 11.53 (o), 11.48 (o).

IR (Neat) 3404 (br), 2926 (m), 2866 (m), 1612 (w), 1586 (w), 1513 (m), 1088 (s), 1027 (vs) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{28}\text{H}_{42}\text{O}_7\text{NaSi}$, 541.2598, found 541.2605.

General procedure for the $\text{VO}(\text{OTf})_2$ catalysed acetone formation.



(3a*R*,4*S*,8*S*,9a*R*)-4-((Benzyloxy)methyl)-6,6-diisopropyl-8-(((4-methoxybenzyl)oxy)methyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3,2]dioxasilocine (20)

To a solution of **17** (0.268 g, 0.52 mmol) in MeCN (2.5 mL) was added 2,2-dimethoxypropane (6.40 mL, 51.6 mmol) and vanadyl triflate (0.028 g, 0.077 mmol). After *ca.* 20 min (TLC control) the reaction mixture was quenched with saturated aqueous NaHCO_3 and partitioned between DCM and water. Phases were separated and the aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /petroleum ether – 1:10, 1:8, 1:7) afforded acetone **20** (0.262 g, 0.47 mmol, 91% yield) as a colourless oil.

$R_f = 0.74$ (Et_2O /hexanes – 2:1).

$[\alpha]_D^{20} -35.9$ (*c* 0.5, CHCl_3).

^1H NMR (500 MHz, CDCl_3) δ 7.35-7.28 (m, 4H), 7.27-7.22 (m, 3H), 6.87-6.84 (m, 2H), 4.59 (d, A of AB, $J_{AB} = 12.8$ Hz, 1H), 4.57 (d, B of AB, $J_{AB} = 13.0$ Hz, 1H),

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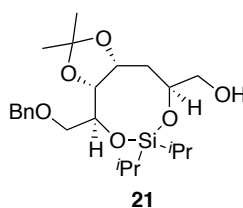
4.54 (d, A of AB, $J_{AB} = 11.7$ Hz, 1H), 4.47 (d, B of AB, $J_{AB} = 11.7$ Hz, 1H), 4.35 (ddd, $J = 11.2, 4.1, 2.4$ Hz, 1H), 4.29 (app. ddt, $J = 11.0, 6.3, 2.0$ Hz, 1H), 4.15-4.09 (m, 2H), 3.78 (s, 3H), 3.75 (dd, A of ABX, $J_{AB} = 10.2$ Hz, $J_{AX} = 1.6$ Hz, 1H), 3.60 (dd, B of ABX, $J_{AB} = 10.1$ Hz, $J_{BX} = 5.3$ Hz, 1H), 3.51 (dd, A of ABX, $J_{AB} = 9.7$ Hz, $J_{AX} = 5.8$ Hz, 1H), 3.45 (dd, B of ABX, $J_{AB} = 9.7$ Hz, $J_{BX} = 7.1$ Hz, 1H), 3.36 (ddd, A of ABXY, $J_{AB} = 14.7$ Hz, $J_{AX} = 11.2$ Hz, $J_{AY} = 5.9$ Hz, 1H), 2.11 (app. dt, B of ABX₂, $J_{AB} = 14.7$ Hz, $J_{BX} = 2.3$ Hz, 1H), 1.35 (s, 3H), 1.30 (s, 3H), 1.08-1.03 (m, 7H), 0.98 (d, $J = 8.8$ Hz, 3H), 0.97 (d, $J = 8.8$ Hz, 3H), 0.95-0.89 (m, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 159.28 (e), 138.85 (e), 130.57 (e), 129.25 (o), 128.28 (o), 127.63 (o), 127.41 (o), 113.91 (o), 106.96 (e), 77.91 (o), 73.60 (o), 73.42 (e), 73.09 (e), 73.02 (e), 72.72 (e), 71.52 (o), 68.56 (o), 55.35 (o), 32.32 (e), 28.33 (o), 25.96 (o), 17.75 (o), 17.53 (o), 17.31 (o), 13.20 (o), 12.44 (o).

IR (Neat) 2939 (m), 2865 (m), 1612 (w), 1586 (w), 1100 (s), 1037 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₂₈H₄₀O₅NaSi 581.2908, found 581.2911.

General procedure for the chemoselective PMB ether deprotection.



((3aR,4S,8S,9aR)-4-((Benzyloxy)methyl)-6,6-diisopropyl-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-e][1,3,2]dioxasilocin-8-yl)methanol (21)

To a cooled to -78 °C solution of **20** (0.262 g, 0.47 mmol) and benzenethiol (0.058 mL, 0.56 mmol) in DCM (2.6 mL) was tin(II) chloride (0.52 mL, 1 M in DCM, 0.52 mmol). After *ca.* 30 min (TLC control) the reaction mixture was quenched with

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saturated aqueous NaHCO_3 , warmed to room temperature and partitioned between DCM and water. Phases were separated and aqueous layer was washed with DCM (2x). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /hexanes – 1:4, 1:3, 1:2) afforded the primary alcohol **21** (0.166 g, 0.38 mmol, 81% yield) as a colourless oil.

$R_f = 0.12$ (Et_2O /hexanes – 1:2).

$[\alpha]_D^{20} -23.5$ (c 0.5, CHCl_3).

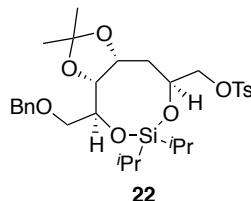
^1H NMR (500 MHz, CDCl_3) δ 7.36-7.31 (m, 4H), 7.27-7.21 (m, 1H), 4.62 (d, A of AB, $J_{AB} = 13.1$ Hz, 1H), 4.59 (d, B of AB, $J_{AB} = 12.9$ Hz, 1H), 4.40 (ddd, $J = 10.9$, 4.8, 2.1 Hz, 1H), 4.22 (dddd, $J = 8.1$, 6.1, 4.1, 2.0 Hz, 1H), 4.17 (dd, A of ABX, $J_{AB} = 10.0$ Hz, $J_{AX} = 4.9$ Hz, 1H), 4.12 (ddd, B of ABXY, $J_{AB} = 10.0$ Hz, $J_{BX} = 5.5$ Hz, $J_{BY} = 1.9$ Hz, 1H), 3.77 (dd, A of ABX, $J_{AB} = 10.2$ Hz, $J_{AX} = 1.9$ Hz, 1H), 3.67 (ddd, A of ABXY, $J_{AB} = 10.3$ Hz, $J_{AX} = 8.9$ Hz, $J_{AY} = 1.4$ Hz, 1H), 3.63 (dd, B of ABX, $J_{AB} = 10.2$ Hz, $J_{BX} = 5.4$ Hz, 1H), 3.54 (ddd, B of ABXY, $J_{AB} = 10.6$ Hz, $J_{BX} = 9.0$ Hz, $J_{BY} = 4.0$ Hz, 1H), 2.42 (ddd, A of ABXY, $J_{AB} = 15.1$ Hz, $J_{AX} = 10.9$ Hz, $J_{AY} = 6.2$ Hz, 1H), 2.17 (dd, $J = 8.9$, 2.5 Hz, 1H), 1.90 (app. dt, B of ABX_2 , $J_{AB} = 15.1$ Hz, $J_{BX} = 2.1$ Hz, 1H), 1.36 (s, 3H), 1.33 (s, 3H), 1.16-1.11 (m, 1H), 1.09 (d, $J = 7.6$ Hz, 3H), 1.07 (d, $J = 6.3$ Hz, 3H), 0.95-0.89 (m, 7H).

^{13}C NMR (125 MHz, CDCl_3) δ 138.72 (e), 128.30 (o), 127.64 (o), 127.46 (o), 107.22 (e), 77.74 (o), 73.80 (o), 73.45 (e), 72.94 (e), 71.41 (o), 69.72 (o), 66.38 (e), 32.64 (e), 28.29 (o), 25.90 (o), 17.69 (o), 17.56 (o), 17.44 (o), 17.35 (o), 13.07 (o), 12.35 (o).

IR (Neat) 3461 (br), 2941 (m), 2867 (m), 1497 (w), 1462 (m), 1153 (s), 1102 (s), 1040 (s) cm^{-1} .

HRMS (ESI, $[M+Na]^+$) calcd for $C_{38}H_{38}O_6NaSi$, 461.2355, found 461.2335.

General procedure for tosylation.



((3a*R*,4*S*,8*S*,9a*R*)-4-((Benzyloxy)methyl)-6,6-diisopropyl-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3,2]dioxasilocin-8-yl)methyl 4-methylbenzenesulfonate (22)

To a solution of **21** (0.166 g, 0.38 mmol) in DCM (2 mL) was added sequentially TsCl (0.108 g, 0.59 mmol), Et₃N (0.132 mL, 0.95 mmol) and DMAP (4.63 mg, 0.038 mmol). After *ca.* 16 h (TLC control) the reaction mixture was quenched with saturated aqueous NaHCO₃ and partitioned between EtOAc and water. Phases were separated and the aqueous layer was washed with EtOAc (2x). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, EtOAc/hexanes – 1:8, 1:7) afforded tosylate **22** (0.225 g, 0.390 mmol, 100%) as a colourless oil.

R_f = 0.51 (Et₂O/hexanes – 1:1).

$[\alpha]_D^{20}$ –22.7 (*c* 0.5, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.81-7.79 (m, 2H), 7.35-7.30 (m, 6H), 7.27-7.24 (m, 1H), 4.59 (d, A of AB, J_{AB} = 12.5 Hz, 1H), 4.56 (d, B of AB, J_{AB} = 12.4 Hz, 1H), 4.37 (app. dq, J = 6.2, 2.5 Hz, 1H), 4.23 (ddd, J = 11.1, 4.7, 2.2 Hz, 1H), 4.10 (dd, A of ABX, J_{AB} = 10.0 Hz, J_{AX} = 4.8 Hz, 1H), 4.07-4.04 (m, 1H), 4.06 (dd, B of ABX, J_{AB} = 9.9 Hz, J_{BX} = 6.5 Hz, 1H), 3.96 (dd, B of ABX, J_{AB} = 9.9 Hz, J_{BX} = 6.0 Hz, 1H), 3.73 (dd, A of ABX, J_{AB} = 10.2 Hz, J_{AX} = 1.9 Hz, 1H), 3.59 (dd, B of ABX, J_{AB}

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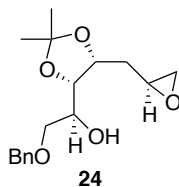
= 10.2 Hz, J_{BX} = 5.4 Hz, 1H), 2.44 (s, 3H), 2.36 (ddd, A of ABXY, J_{AB} = 15.2 Hz, J_{AX} = 11.1 Hz, J_{AY} = 6.0 Hz, 1H), 1.95 (app. dt, B of ABX₂, J_{AB} = 15.1 Hz, J_{BX} = 2.3 Hz, 1H), 1.34 (s, 3H), 1.28 (s, 3H), 1.05-0.99 (m, 7H), 0.96-0.88 (m, 1H), 0.95 (d, J = 6.0 Hz, 3H), 0.93 (d, J = 5.6 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 144.96 (e), 138.69 (e), 133.06 (e), 130.00 (o), 128.28 (o), 128.00 (o), 127.61 (o), 127.45 (o), 107.26 (e), 77.65 (o), 73.42 (e), 73.19 (o), 72.87 (e), 71.98 (e), 71.40 (o), 66.90 (o), 32.07 (e), 28.26 (o), 25.87 (o), 21.74 (o), 17.57 (o), 17.36 (o), 17.32 (o), 17.13 (o), 12.97 (o), 12.27 (o).

IR (Neat) 2942 (m), 2867 (m), 1598 (w), 1496 (w), 1454 (m), 1368 (s), 1177 (s), 1098 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₃₀H₄₄O₈NaSiS 615.2424, found 615.2428.

General procedure for the hydroxy epoxide formation.



(S)-2-(Benzyloxy)-1-((4S,5R)-2,2-dimethyl-5-((S)-oxiran-2-ylmethyl)-1,3-dioxolan-4-yl)ethanol (24)

To a solution of **22** (0.2274 g, 0.384 mmol) in THF (2.1 mL) was added TBAF (0.84 mL, 1 M in THF, 0.84 mmol) at 0 °C. After *ca.* 30 min (TLC control) the reaction mixture was quenched with saturated aqueous NaHCO₃ and partitioned between EtOAc and water. Phases were separated and the aqueous layer was washed with EtOAc (2x). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel,

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EtOAc/hexanes – 1:3, 1:2.5, 1:2) afforded the hydroxy epoxide **24** (0.111 g, 0.360 mmol, 94%) as a colourless oil.

$R_f = 0.6$ (EtOAc/hexanes – 1:1).

$[\alpha]_D^{20} -1.0$ (c 0.5, CHCl_3).

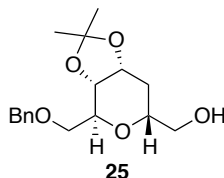
^1H NMR (500 MHz, CDCl_3) δ 7.37-7.29 (m, 5H), 4.57 (s, 2H), 4.34 (app. dt, A of ABX_2 , $J_{AB} = 8.5$ Hz, $J_{AX} = 5.4$ Hz, 1H), 4.00 (dd, B of ABX , $J_{AB} = 9.4$ Hz, $J_{BX} = 5.7$ Hz, 1H), 3.81 (dddd, $J = 9.1, 6.8, 4.5, 2.5$ Hz, 1H), 3.74 (dd, A of ABX , $J_{AB} = 9.5$ Hz, $J_{AX} = 2.8$ Hz, 1H), 3.57 (dd, B of ABX , $J_{AB} = 9.5$ Hz, $J_{BX} = 6.6$ Hz, 1H), 3.15 (app. tt, $J = 5.6, 4.0$ Hz, 1H), 2.77 (app. t, A of AM_2 , $J_{AM} = 4.5$ Hz, 1H), 2.60 (d, $J = 4.7$ Hz, 1H), 2.57 (dd, M of AMX , $J_{AM} = 5.0$ Hz, $J_{MX} = 2.7$ Hz, 1H), 1.99 (app. dt, A of ABX_2 , $J_{AB} = 14.2$ Hz, $J_{AX} = 5.4$ Hz, 1H), 1.95 (app. dt, B of ABX_2 , $J_{AB} = 14.3$ Hz, $J_{BX} = 4.9$ Hz, 1H), 1.42 (s, 3H), 1.33 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 137.90 (e), 128.57 (o), 127.96 (o), 127.84 (o), 108.56 (e), 77.16 (o), 75.44 (o), 73.52 (e), 71.98 (e), 68.37 (o), 50.31 (o), 46.88 (e), 32.56 (e), 28.25 (o), 25.76 (o).

IR (Neat) 3448 (br), 2986 (w), 2932 (w), 1454 (w), 1217 (s), 1052 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{17}\text{H}_{24}\text{O}_5\text{Na}$ 331.1521, found 331.1524.

General procedure for THP formation.



((3a*R*,4*S*,6*R*,7a*R*)-4-((Benzyloxy)methyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl)methanol (25)

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To a cooled to 0 °C solution of the epoxy alcohol **24** (0.096 g, 0.311 mmol) in DCM (4.5 mL) added CSA (7.23 mg, 0.031 mmol). After *ca.* 40 min (TLC control) the reaction mixture was quenched with 50 μ L Et₃N, concentrated and purified by flush chromatography (SiO₂, EtOAc/hexanes – 1:2, 1:1) to afford the *anti*-THP **25** (0.088 g, 0.285 mmol, 92% yield) as a colourless oil.

FC (SiO₂, EtOAc/hexanes – 1:2.5, 1:2, 1:1.5).

R_f = 0.3 (EtOAc/hexanes – 1:1).

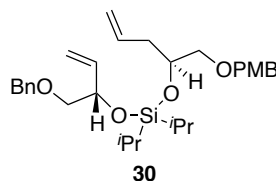
$[\alpha]_{\text{D}}^{20}$ –34.8 (*c* 0.25, CHCl₃).

¹H NMR (500 MHz, C₆D₆) δ 7.28-7.26 (m, 2H), 7.17-7.14 (m, 2H), 7.09-7.06 (m, 1H), 4.38 (d, A of AB, J_{AB} = 12.2 Hz, 1H), 4.34 (d, B of AB, J_{AB} = 12.2 Hz, 1H), 4.05 (app. dt, A of ABX₂, J_{AB} = 8.7 Hz, J_{AX} = 6.4 Hz, 1H), 4.02 (dd, J = 7.1, 6.3, 2.3 Hz, 1H), 3.89 (app. t, B of AB₂, J_{AB} = 6.8 Hz, 1H), 3.66 (ddd, J = 6.6, 4.4, 3.7 Hz, 1H), 3.63 (dd, A of ABX, J_{AB} = 10.4 Hz, J_{AX} = 2.6 Hz, 1H), 3.58-3.54 (m, 1H), 3.48 (dd, B of ABX, J_{AB} = 10.4 Hz, J_{BX} = 6.1 Hz, 1H), 3.43-3.41 (m, 1H), 3.01 (br s, 1H), 1.68 (ddd, A of ABXY, J_{AB} = 13.7 Hz, J_{AX} = 9.7 Hz, J_{AY} = 9.0 Hz, 1H), 1.62 (ddd, B of ABXY, J_{AB} = 13.7 Hz, J_{BX} = 6.7 Hz, J_{BY} = 4.6 Hz, 1H), 1.43 (s, 3H), 1.22 (s, 3H).

¹³C NMR (125 MHz, C₆D₆) δ 138.75 (e), 128.65 (o), 127.92 (o), 127.83 (o), 108.64 (e), 73.59 (e), 72.68 (o), 72.30 (o), 71.92 (o), 71.78 (e), 71.68 (o), 64.93 (e), 29.31 (e), 27.99 (o), 25.59 (o).

IR (Neat) 3434 (br), 2985 (w), 2933 (w), 2871 (w), 1497 (w), 1454 (w), 1052 (s) cm^{–1}.

HRMS (ESI, [M+Na]⁺) calcd for C₁₇H₂₄O₅Na 331.1527, found 331.1521.



(4*S*,8*S*)-4-Allyl-6,6-diisopropyl-1-(4-methoxyphenyl)-11-phenyl-8-vinyl-2,5,7,10-tetraoxa-6-silaundecane (30)

Prepared according the general procedure for the temporary silicon tether formation on 5 mmol scale with 82% yield.

Colour and state: Colourless oil.

FC (SiO₂, Et₂O/hexanes – 1:16).

R_f = 0.4 (Et₂O/hexanes – 1:5).

$[\alpha]_{\text{D}}^{20}$ –11.4 (*c* 1.0, CHCl₃).

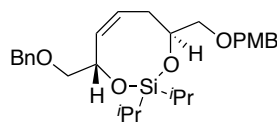
¹H NMR (500 MHz, C₆D₆) δ 7.29-7.27 (m, 2H), 7.23-7.20 (m, 2H), 7.19-7.16 (m, 2H), 7.10-7.07 (m, 1H), 6.80-6.77 (m, 2H), 5.96 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 5.94 (ddd, *J* = 17.0, 10.7, 6.1 Hz, 1H), 5.36 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.13-5.04 (m, 3H), 4.69 (app. ddt, *J* = 11.8, 5.3, 1.2 Hz, 1H), 4.38 (d, A of AB, *J*_{AB} = 12.3 Hz, 1H), 4.36 (d, B of AB, *J*_{AB} = 12.5 Hz, 1H), 4.35 (s, 2H), 4.32 (quintet, *J* = 5.6 Hz, 1H), 3.53 (dd, A of ABX, *J*_{AB} = 9.4 Hz, *J*_{AX} = 6.2 Hz, 1H), 3.52 (dd, A of ABX, *J*_{AB} = 9.4 Hz, *J*_{AX} = 5.5 Hz, 1H), 3.43 (dd, B of ABX, *J*_{AB} = 9.4 Hz, *J*_{BX} = 5.3 Hz, 1H), 3.37 (dd, B of ABX, *J*_{AB} = 9.4 Hz, *J*_{BX} = 5.3 Hz, 1H), 3.31 (s, 3H), 2.50 (app. dt, A of ABX₂, *J*_{AB} = 13.9 Hz, *J*_{AX} = 6.4 Hz, 1H), 2.42 (app. dt, B of ABX₂, *J*_{AB} = 13.6 Hz, *J*_{BX} = 6.7 Hz, 1H), 1.20-1.17 (m, 12H), 1.15-1.05 (m, 2H).

¹³C NMR (125 MHz, C₆D₆) δ 159.77 (e), 139.26 (o), 139.07 (e), 135.12 (o), 131.10 (e), 129.52 (o), 128.55 (o), 127.84 (o), 127.69 (o), 117.24 (e), 115.11 (e), 114.07 (o), 75.55 (e), 74.00 (e), 73.46 (e), 73.21 (e), 72.86 (o), 71.31 (o), 54.79 (o), 39.76 (e), 17.86 (o), 13.32 (o).

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IR (Neat) 3072 (w), 2943 (m), 2865 (m), 1642 (w), 1612 (w), 1586 (w), 1187 (vs), 1036 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{30}\text{H}_{44}\text{O}_5\text{NaSi}$ 535.2856, found 535.2839.



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(4*S*,8*S*,*Z*)-8-((Benzyloxy)methyl)-2,2-diisopropyl-4-(((4-methoxybenzyl)oxy)methyl)-5,8-dihydro-4*H*-1,3,2-dioxasilocine (31)

Prepared according the general procedure for the temporary silicon-tethered ring-closing metathesis on 0.497 mmol scale with 98% yield.

Colour and state: Colourless oil.

FC (SiO_2 , Et_2O /hexanes – 1:12, 1:10).

R_f = 0.63 (Et_2O /hexanes – 1:1).

$[\alpha]_{\text{D}}^{20}$ –23.5 (*c* 1.0, CHCl_3).

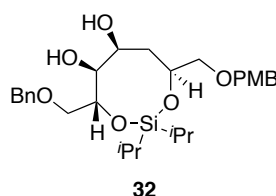
^1H NMR (500 MHz, C_6D_6) δ 7.31-7.30 (m, 2H), 7.23-7.20 (m, 2H), 7.20-7.16 (m, 2H), 7.10-7.07 (m, 1H), 6.81-6.79 (m, 2H), 5.80 (dd, $J = 10.8, 8.1$ Hz, 1H), 5.59 (dt, $J = 10.9, 8.7$ Hz, 1H), 4.74 (app. dt, $J = 7.9, 5.6$ Hz, 1H), 4.44 (d, A of AB, $J_{AB} = 12.4$ Hz, 1H), 4.41 (d, B of AB, $J_{AB} = 12.3$ Hz, 1H), 4.40 (d, A of AB, $J_{AB} = 11.7$ Hz, 1H), 4.36 (d, B of AB, $J_{AB} = 11.7$ Hz, 1H), 4.01 (dddd, $J = 9.0, 7.3, 5.6, 1.7$ Hz, 1H), 3.59 (dd, A of ABX, $J_{AB} = 9.7$ Hz, $J_{AX} = 6.1$ Hz, 1H), 3.50 (dd, A of ABX, $J_{AB} = 9.0$ Hz, $J_{AX} = 5.4$ Hz, 1H), 3.48 (dd, B of ABX, $J_{AB} = 9.6$ Hz, $J_{BX} = 5.3$ Hz, 1H), 3.32 (s, 3H), 3.30 (dd, B of ABX, $J_{AB} = 9.2$ Hz, $J_{BX} = 6.9$ Hz, 1H), 2.47 (ddd, A of ABXY, $J_{AB} = 13.6$ Hz, $J_{AX} = 8.5$ Hz, $J_{AY} = 1.7$ Hz, 1H), 2.26 (app. dtd, B of ABX₂Y, $J_{AB} =$

13.6 Hz, $J_{BX} = 8.8$ Hz, $J_{BY} = 0.9$ Hz, 1H), 1.21 (d, $J = 7.3$ Hz, 3H), 1.20 (d, $J = 7.3$ Hz, 3H), 1.15 (d, $J = 6.8$ Hz, 3H), 1.10 (d, $J = 6.5$ Hz, 3H), 1.10-1.02 (m, 2H).

^{13}C NMR (125 MHz, C_6D_6) δ 159.77 (e), 139.34 (e), 134.55 (o), 131.10 (e), 129.92 (o), 129.39 (o), 128.53 (o), 127.67 (o), 127.59 (o), 114.11 (o), 74.61 (e), 74.19 (e), 73.43 (e), 73.35 (o), 73.19 (e), 68.37 (o), 54.80 (o), 32.84 (e), 17.94 (o), 17.87 (o), 17.83 (o), 17.74 (o), 13.38 (o), 12.96 (o).

IR (Neat) 3003 (w), 2942 (m), 2864 (m), 1612 (w), 1586 (w), 1513 (s), 1092 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{28}\text{H}_{40}\text{O}_5\text{NaSi}$ 507.2543, found 507.2555.



(4R,5S,6S,8S)-4-((Benzyloxy)methyl)-2,2-diisopropyl-8-(((4-methoxybenzyloxy)methyl)-1,3,2-dioxasilocane-5,6-diol (32)

Prepared according the general procedure for the dihydroxylation of cyclic silaketals on 3.97 mmol scale with 92% yield.

Colour and state: Colourless oil.

FC (SiO_2 , Et_2O /hexanes – 1:1, 2:1, 3:1, 20:1).

R_f = 0.07 (Et_2O /hexanes – 1:1).

$[\alpha]_{\text{D}}^{20} -36.5$ (c 1.0, CHCl_3).

^1H NMR (500 MHz, CDCl_3) δ 7.37-7.24 (m, 7H), 6.88-6.86 (m, 2H), 4.60 (d, A of AB, $J_{AB} = 12.1$ Hz, 1H), 4.59 (d, B of AB, $J_{AB} = 12.2$ Hz, 1H), 4.51 (d, A of AB, $J_{AB} = 11.7$ Hz, 1H), 4.48 (d, B of AB, $J_{AB} = 11.8$ Hz, 1H), 4.15 (dddd, $J = 10.6, 6.6, 5.6, 0.9$ Hz, 1H), 4.03 (app. td, $J = 7.5, 2.0$ Hz, 1H), 3.96 (ddd, A of ABXY, $J_{AB} = 9.1$ Hz,

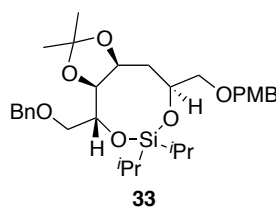
Chapter 6

$J_{AX} = 6.3$ Hz, $J_{AY} = 4.3$ Hz, 1H), 3.91 (app. dt, B of ABX₂, $J_{AB} = 9.1$ Hz, $J_{BX} = 2.0$ Hz, 1H), 3.80 (s, 3H), 3.74 (dd, A of ABX, $J_{AB} = 9.6$ Hz, $J_{AX} = 4.4$ Hz, 1H), 3.63 (dd, B of ABX, $J_{AB} = 9.5$ Hz, $J_{BX} = 6.5$ Hz, 1H), 3.47 (dd, A of ABX, $J_{AB} = 9.7$ Hz, $J_{AX} = 5.5$ Hz, 1H), 3.34 (dd B of ABX, $J_{AB} = 9.7$ Hz, $J_{BX} = 6.2$ Hz, 1H), 3.24 (br s, 1H), 2.54 (d, $J = 7.9$ Hz, 1H), 2.17 (ddd, A of ABXY, $J_{AB} = 15.5$ Hz, $J_{AX} = 10.3$ Hz, $J_{AY} = 7.8$ Hz, 1H), 1.71 (d, B of AB, $J_{AB} = 15.2$ Hz, 1H), 1.05-1.02 (m, 7H), 1.00-0.84 (m, 7H).

¹³C NMR (125 MHz, CDCl₃) δ 159.12 (e), 137.61 (e), 130.50 (e), 129.16 (o), 128.51 (o), 127.90 (o), 127.75 (o), 113.76 (o), 76.01 (o), 74.61 (e), 73.94 (e), 73.73 (e), 73.02 (e), 72.99 (o), 72.44 (o), 69.62 (o), 55.29 (o), 36.81 (e), 17.65 (o), 17.46 (o), 17.38 (o), 17.31 (o), 12.50 (o), 11.73 (o).

IR (Neat) 3419 (br), 2924 (m), 2865 (m), 1612 (w), 1586 (w), 1513 (m), 1102 (s), 1061 (s), 1033 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₂₈H₄₂O₇NaSi 541.2598, found 541.2584.



((3a*S*,4*R*,8*S*,9a*S*)-4-((Benzyloxy)methyl)-6,6-diisopropyl-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3,2]dioxasilocin-8-yl)methanol
(33)

Prepared according the general procedure for the VO(OTf)₂ catalysed acetone formation on 1.23 mmol scale with 100% yield.

Colour and state: Colourless oil.

FC (SiO₂, Et₂O/hexanes – 1:4, 1:3, 1:2).

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R_f = 0.3 (Et₂O/hexanes – 1:1).

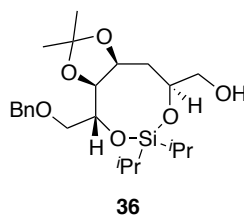
$[\alpha]_{\text{D}}^{20}$ –12.0 (*c* 0.5, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.37-7.31 (m, 4H), 7.29-7.25 (m, 1H), 4.64 (d, A of AB, *J*_{AB} = 12.3 Hz, 1H), 4.59 (d, B of AB, *J*_{AB} = 12.3 Hz, 1H), 4.29 (dd, A of ABX, *J*_{AB} = 10.8 Hz, *J*_{AX} = 3.7 Hz, 1H), 4.22-4.17 (m, 2H), 3.96 (app. td, *J* = 8.2, 3.8 Hz, 1H), 3.73 (dd, A of ABX, *J*_{AB} = 10.3 Hz, *J*_{AX} = 1.4 Hz, 1H), 3.65 (dd, B of ABX, *J*_{AB} = 10.4 Hz, *J*_{BX} = 5.0 Hz, 1H), 3.54 (ddd, A of ABXY, *J*_{AB} = 10.9 Hz, *J*_{AX} = 8.8 Hz, *J*_{AY} = 3.6 Hz, 1H), 3.46 (ddd, B of ABXY, *J*_{AB} = 10.9 Hz, *J*_{BX} = 7.7 Hz, *J*_{BY} = 3.4 Hz, 1H), 2.10 (dd, *J* = 9.2, 4.1 Hz, 1H), 2.05 (ddd, A of ABXY, *J*_{AB} = 15.5 Hz, *J*_{AX} = 10.8 Hz, *J*_{AY} = 9.1 Hz, 1H), 1.57 (d, B of AB, *J*_{AB} = 15.4 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H), 1.09-1.04 (m, 7H), 1.03-0.98 (m, 7H).

¹³C NMR (125 MHz, CDCl₃) δ 138.69 (e), 128.35 (o), 127.67 (o), 127.53 (o), 108.38 (e), 79.38 (o), 77.38 (o), 73.62 (e), 73.06 (e), 72.88 (o), 69.65 (o), 67.80 (e), 37.68 (e), 28.38 (o), 25.99 (o), 17.82 (o), 17.49 (o), 17.45 (o), 17.30 (o), 12.77 (o), 12.04 (o).

IR (Neat) 3689 (br), 2941 (m), 2867 (m), 1497 (w), 1464 (w), 1455 (w), 1117 (s), 1083 (s), 1065 (s) 1031 (s) cm^{–1}.

HRMS (ESI, [M+Na]⁺) calcd for C₂₃H₃₈O₆NaSi 461.2335, found 461.2329.



((3aS,4R,8S,9aS)-4-((Benzyloxy)methyl)-6,6-diisopropyl-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-e][1,3,2]dioxasilocin-8-yl)methanol
(36)

Prepared according the general procedure for the chemoselective PMB ether deprotection on 1.056 mmol scale with 96% yield.

Colour and state: Colourless oil.

FC (SiO₂, EtOAc/hexanes – 1:8, 1:7).

R_f = 0.12 (Et₂O/hexanes – 1:2).

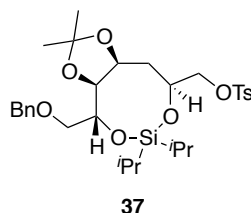
[α]_D²⁰ –12.0 (c 0.5, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.37-7.31 (m, 4H), 7.29-7.25 (m, 1H), 4.64 (d, A of AB, *J*_{AB} = 12.3 Hz, 1H), 4.59 (d, B of AB, *J*_{AB} = 12.3 Hz, 1H), 4.29 (dd, A of ABX, *J*_{AB} = 10.8 Hz, *J*_{AX} = 3.7 Hz, 1H), 4.22-4.17 (m, 2H), 3.96 (app. td, *J* = 8.2, 3.8 Hz, 1H), 3.73 (dd, A of ABX, *J*_{AB} = 10.3 Hz, *J*_{AX} = 1.4 Hz, 1H), 3.65 (dd, B of ABX, *J*_{AB} = 10.4 Hz, *J*_{BX} = 1.4 Hz, 1H), 3.54 (ddd, A of ABXY, *J*_{AB} = 10.9 Hz, *J*_{AX} = 8.8 Hz, *J*_{AY} = 3.6 Hz, 1H), 3.46 (ddd, B of ABXY, *J*_{AB} = 10.9 Hz, *J*_{BX} = 7.7 Hz, *J*_{BY} = 3.4 Hz, 1H), 2.10 (dd, *J* = 9.2, 4.1 Hz, 1H), 2.05 (ddd, A of ABXY, *J*_{AB} = 15.5 Hz, *J*_{AX} = 10.8 Hz, *J*_{AY} = 9.1 Hz, 1H), 1.57 (d, B of AB, *J*_{AB} = 15.4 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H), 1.09-1.04 (m, 7H), 1.03-0.98 (m, 7H).

¹³C NMR (125 MHz, CDCl₃) δ 138.69 (e), 128.35 (o), 127.67 (o), 127.53 (o), 108.38 (e), 79.38 (o), 77.38 (o), 73.62 (e), 73.06 (e), 72.88 (o), 69.65 (o), 67.80 (e), 37.68 (e), 28.38 (o), 25.99 (o), 17.82 (o), 17.49 (o), 17.45 (o), 17.30 (o), 12.77 (o), 12.04 (o).

IR (Neat) 3468 (br), 2941 (m), 2867 (m), 1497 (w), 1464 (w), 1117 (s), 1182 (s), 1031 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{38}\text{H}_{38}\text{O}_6\text{NaSi}$ 461.2329, found 461.2335.



((3a*S*,4*R*,8*S*,9a*S*)-4-((Benzyloxy)methyl)-6,6-diisopropyl-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3,2]dioxasilocin-8-yl)methyl 4-methylbenzenesulfonate (37)

Prepared according the general procedure for tosylation on 0.958 mmol scale with 97% yield.

Colour and state: Colourless oil.

FC (SiO_2 , EtOAc/hexanes – 1:8, 1:7).

R_f = 0.9 (EtOAc/hexanes – 1:1).

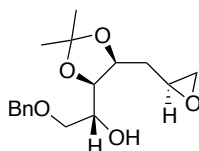
$[\alpha]_{\text{D}}^{20}$ –14.3 (*c* 1.0, CHCl_3).

^1H NMR (500 MHz, CDCl_3) δ 7.80-7.78 (m, 2H), 7.35-7.30 (m, 6H), 7.28-7.24 (m, 1H), 4.62 (d, A of AB, J_{AB} = 12.3 Hz, 1H), 4.56 (d, B of AB, J_{AB} = 12.3 Hz, 1H), 4.21-4.16 (m, 2H), 4.11 (ddd, J = 9.5, 5.2, 2.1 Hz, 1H), 4.02 (app. dt, J = 8.8, 5.8 Hz, 1H), 3.97 (dd, A of ABX, J_{AB} = 9.7 Hz, J_{AX} = 6.4 Hz, 1H), 3.87 (dd, B of ABX, J_{AB} = 9.7 Hz, J_{BX} = 5.2 Hz, 1H), 3.70 (dd, A of ABX, J_{AB} = 10.4 Hz, J_{AX} = 2.1 Hz, 1H), 3.62 (dd, B of ABX, J_{AB} = 10.4 Hz, J_{BX} = 5.2 Hz, 1H), 2.44 (s, 3H), 1.95 (ddd, A of ABXY, J_{AB} = 15.2 Hz, J_{AX} = 10.3 Hz, J_{AY} = 9.2 Hz, 1H), 1.62 (d, B of AB, J_{AB} = 15.1 Hz, 1H), 1.33 (s, 3H), 1.30 (s, 3H), 1.03-0.99 (m, 1H), 1.02 (s, 3H), 1.01 (s, 3H), 0.96-0.89 (m, 1H), 0.95 (d, J = 5.5 Hz, 3H), 0.92 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 144.94 (e), 138.64 (e), 133.08 (e), 129.96 (o), 128.32 (o), 128.05 (o), 127.62 (o), 127.49 (o), 108.35 (e), 79.18 (o), 77.26 (o), 73.56 (e), 73.43 (e), 72.94 (e), 69.84 (o), 69.51 (o), 37.42 (e), 28.32 (o), 25.92 (o), 21.73 (o), 17.66 (o), 17.29 (o), 17.23 (o), 17.08 (o), 12.58 (o), 11.86 (o).

IR (Neat) 2943 (w), 2867 (w), 1599 (w), 1497 (w), 1464 (w), 1454 (w), 1365 (m), 1177 (s), 969 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{30}\text{H}_{44}\text{O}_8\text{NaSiS}$ 615.2424, found 615.2425.



(*R*)-2-(Benzyloxy)-1-(((4*R*,5*S*)-2,2-dimethyl-5-((*S*)-oxiran-2-ylmethyl)-1,3-dioxolan-4-yl)ethanol (38)

Prepared according the general procedure for the hydroxy epoxide formation on 0.336 mmol scale with 84% yield.

Colour and state: Colourless oil.

R_f = 0.6 (EtOAc/hexanes – 1:1).

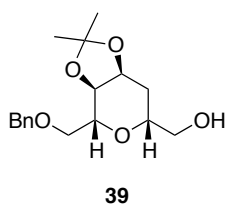
$[\alpha]_D^{20}$ –15.0 (*c* 0.5, CHCl_3).

^1H NMR (500 MHz, CDCl_3) δ 7.37-7.28 (m, 5H), 4.57 (s, 2H), 4.43 (app. dt, A of ABX_2 , J_{AB} = 8.0 Hz, J_{AX} = 5.7 Hz, 1H), 4.01 (dd, B of ABX , J_{AB} = 9.3 Hz, J_{BX} = 5.8 Hz, 1H), 3.78 (dddd, J = 9.2, 7.2, 4.8, 2.7 Hz, 1H), 3.73 (dd, A of ABX , J_{AB} = 9.5 Hz, J_{AX} = 2.8 Hz, 1H), 3.57 (dd, B of ABX , J_{AB} = 9.5 Hz, J_{BX} = 6.5 Hz, 1H), 3.14 (app. tdd, J = 5.9, 3.7, 2.7 Hz, 1H), 2.83 (dd, A of AMX , J_{AM} = 5.0 Hz, J_{AX} = 4.1 Hz, 1H), 2.62 (d, J = 4.9 Hz, 1H), 2.57 (dd, M of AMX , J_{AM} = 5.0 Hz, J_{MX} = 2.7 Hz, 1H), 1.89 (app. dt, A of ABX_2 , J_{AB} = 14.2 Hz, J_{AX} = 6.2 Hz, 1H), 1.85 (app. dt, B of ABX_2 , J_{AB} = 14.0 Hz, J_{BX} = 5.4 Hz, 1H), 1.40 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 137.98 (e), 128.58 (o), 127.95 (o), 127.85 (o), 108.54 (e), 77.15 (o), 75.34 (o), 73.56 (e), 72.02 (e), 68.49 (o), 50.34 (o), 47.94 (e), 33.35 (e), 28.31 (o), 25.76 (o).

IR (Neat) 3455 (br), 2986 (w), 2932 (w), 1454 (w), 1217 (s), 1050 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{17}\text{H}_{24}\text{O}_5\text{Na}$ 331.1521, found 331.1528.



((3a*S*,4*R*,6*R*,7a*S*)-4-((Benzyloxy)methyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl)methanol (39)

Prepared according the general procedure for THP formation on 0.221 mmol scale with 87% yield.

Colour and state: Colourless oil.

FC (SiO_2 , EtOAc/hexanes – 1:2.5, 1:2, 1:1.5).

R_f = 0.3 (EtOAc/hexanes – 1:1).

$[\alpha]_{\text{D}}^{20}$ +52.0 (*c* 0.25, CHCl_3).

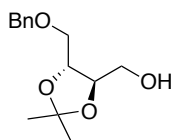
^1H NMR (500 MHz, C_6D_6) δ 7.31-7.29 (m, 2H), 7.16-7.13 (m, 2H), 7.09-7.05 (m, 1H), 4.42 (d, A of AB, J_{AB} = 12.2 Hz, 1H), 4.39 (d, B of AB, J_{AB} = 12.2 Hz, 1H), 4.01 (app. td, J = 4.5, 1.9 Hz, 1H), 3.77 (dd, A of ABX, J_{AB} = 9.0 Hz, J_{AX} = 5.0 Hz, 1H), 3.70 (d, B of AB, J_{AB} = 8.9 Hz, 1H), 3.67 (ddd, J = 11.9, 6.0, 3.0 Hz, 1H), 3.60 (ddd, A of ABXY, J_{AB} = 7.6 Hz, J_{AX} = 5.9 Hz, J_{AY} = 1.6 Hz, 1H), 3.56 (dd, B of ABX, J_{AB} = 10.4 Hz, J_{BX} = 6.0 Hz, 1H), 3.46 (dd, A of ABX, J_{AB} = 11.6 Hz, J_{AX} = 3.3 Hz, 1H), 3.34 (dd, B of ABX, J_{AB} = 11.6 Hz, J_{BX} = 6.3 Hz, 1H), 2.33 (br s, 1H), 1.71

(app. dt, A of ABX, $J_{AB} = 14.8$ Hz, $J_{AX} = 2.2$ Hz, 1H), 1.46 (ddd, B of ABXY, $J_{AB} = 14.9$ Hz, $J_{BX} = 11.8$ Hz, $J_{BY} = 4.0$ Hz, 1H), 1.40 (s, 3H), 1.24 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 138.98 (e), 128.58 (o), 127.92 (o), 127.75 (o), 108.90 (e), 78.04 (o), 73.70 (o), 73.61 (e), 72.25 (o), 71.34 (o), 70.93 (e), 65.54 (e), 28.85 (e), 28.54 (o), 26.45 (o).

IR (Neat) 3435 (br), 2985 (w), 2919 (w), 2873 (w), 1497 (w), 1454 (w), 1081 (s) 1050 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{17}\text{H}_{24}\text{O}_5\text{Na}$ 331.1526, found 331.1521.



44

((4R,5R)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (44)¹⁷

To a solution of diol **43** (8.77 g, 54.1 mmol) in DCM (221 mL) was added sequentially silver(I) oxide (18.81 g, 81.0 mmol) and benzyl bromide (7.12 mL, 59.5 mmol). The reaction mixture was stirred for *ca.* 60 h (TLC control), before it was passed through a pad of silica gel (washed with EtOAc), concentrated *in vacuo* and purified by flush chromatography (silica gel, Et₂O/hexanes – 1:1, 2:1, then EtOAc to recover 2.275 g of unreacted **43**) to afford the benzyl ether **44** (9.1 g, 36.1 mmol, 70%, 90% b.r.s.m.).

Colour and state: Colourless oil.

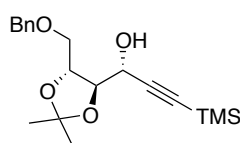
R_f = 0.47 (EtOAc/hexanes – 1:1)

$[\alpha]_{\text{D}}^{20}$ –9.0 (*c* 1.0, CHCl_3), Lit. $[\alpha]_{\text{D}}^{25}$ –8.0 (*c* 0.975, CHCl_3).¹⁷

^1H NMR (500 MHz, CDCl_3) δ 7.37–7.28 (m, 5H), 4.60 (dd, A of AB, $J_{AB} = 12.4$ Hz, 1H), 4.58 (dd, B of AB, $J_{AB} = 12.4$ Hz, 1H), 4.06 (app. dt, A of ABX₂, $J_{AB} = 8.2$ Hz,

$J_{AX} = 5.5$ Hz, 1H), 3.95 (app. dt, B of ABX₂, $J_{AB} = 8.4$ Hz, $J_{BX} = 4.3$ Hz, 1H), 3.77 (app. dt, A of ABX₂, $J_{AB} = 11.7$ Hz, $J_{AX} = 4.5$ Hz, 1H), 3.70-3.65 (m, 1H), 3.68 (dd, A of ABX, $J_{AB} = 10.0$ Hz, $J_{AX} = 5.1$ Hz, 1H), 3.56 (dd, B of ABX, $J_{AB} = 9.8$ Hz, $J_{BX} = 5.8$ Hz, 1H), 2.30 (br s, 1H), 1.42 (s, 3H), 1.41 (s, 3H).

IR (Neat) cm⁻¹ 3444 (w), 2986 (w), 2868 (w), 1454 (m), 1078 (s).



49

(*R*)-1-((4*R*,5*R*)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (49)

To a solution of oxalyl chloride (4.3 mL, 50.3 mmol) in DCM (157 mL) at -78 °C was added DMSO (6.0 mL, 84 mmol) in DCM (12 mL with washings). After *ca.* 30 min alcohol **44** (8.465 g, 33.5 mmol) was added as a solution in DCM (16 mL with washings). After *ca.* 1 hour (TLC control) DIPEA (35.0 mL, 201 mmol) was added and the reaction was stirred for *ca.* 30 min at -78 °C and *ca.* 30 min at room temperature, before it was quenched with pH 7 buffer and partitioned between water and Et₂O. Phases were separated and the aqueous layer was washed with Et₂O (2x). The combined organic layers were washed with water (2x), brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford crude aldehyde **45**, which was used in the next step without purification.

To a cooled to -78 °C solution of trimethylsilylacetylene (10.5 mL, 73.7 mmol) in THF (91 mL) was added ^{*n*}BuLi (26.8 mL, 2.5 M in hexanes, 67.0 mmol). After *ca.* 30 min a premixed solution of Ti(O^{*i*}Pr)₄ (11.5 mL, 37.9 mmol) and TiCl₄ (37.9 mL, 1 M in PhMe, 37.9 mmol) was slowly added over *ca.* 40 min, (*exotherm!*) and the

reaction mixture was stirred for *ca.* 1 hour at that temperature, before it was treated with a solution of crude aldehyde **45** (~33.5 mmol) in THF (27 mL with washings). The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for *ca.* 2 hours and then left to slowly warm up to room temperature. After *ca.* 14 h (TLC control) the reaction mixture was quenched with saturated aqueous NH_4Cl and partitioned between water and Et_2O . Phases were separated and the aqueous layer was washed with Et_2O (2x). The combined organic layers were washed with water, brine, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /hexanes – 1:5, 1:4) afforded the propargylic alcohol **49** (7.91 g, 22.69 mmol, 68% yield) as a brown oil.

$R_f = 0.51$ (Et_2O /hexanes – 1:1).

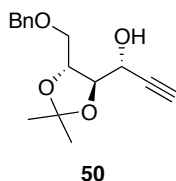
$[\alpha]_D^{20} +11.7$ (*c* 1.0, CHCl_3), Lit. $[\alpha]_D^{20} -2.7$ (*c* 0.47, CCl_4) for *ent.*^[18]

^1H NMR (500 MHz, CDCl_3) δ 7.34-7.33 (m, 4H), 7.30-7.26 (m, 1H), 4.60 (s, 2H), 4.55 (t, $J = 4.1$ Hz, 1H), 4.29 (app. dt, A of ABX_2 , $J_{AB} = 8.5$ Hz, $J_{AX} = 4.4$ Hz, 1H), 4.02 (dd, B of ABX , $J_{AB} = 8.1$ Hz, $J_{BX} = 3.5$ Hz, 1H), 3.73 (dd, AB of ABX , $J_{AB} = 10.3$ Hz, $J_{AX} = 3.9$ Hz, 1H), 3.68 (dd, B of ABX , $J_{AB} = 10.3$ Hz, $J_{BX} = 5.5$ Hz, 1H), 2.62 (d, $J = 5.0$ Hz, 1H), 1.46 (s, 3H), 1.14 (s, 3H), 0.16 (d, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ 137.91 (e), 128.43 (o), 127.72 (o), 127.62 (o), 109.93 (e), 102.12 (e), 92.06 (e), 79.87 (o), 76.27 (o), 73.67 (e), 71.04 (e), 62.66 (o), 27.23 (o), 26.95 (o), -0.26 (o).

IR (Neat) 3434 (w), 2987 (w), 2899 (w), 2176 (w), 1497 (w), 1083 (m) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{19}\text{H}_{28}\text{O}_4\text{NaSi}$ 371.1655, found 371.1654.



(*R*)-1-((4*R*,5*R*)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-yn-1-ol (50)

To a solution of the TMS protected alkyne **49** (24.73 g, 71.0 mmol) in THF (80 mL) was added TBAF (82 mL, 82 mmol) and the reaction mixture was stirred for *ca.* 30 min (TLC control). After that time the reaction quenched with saturated aqueous NH₄Cl and partitioned between water and Et₂O. Phases were separated and the aqueous layer was washed with Et₂O (2x). The combined organic layers were washed with water, brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was used in the next step without further purification. An analytical sample was obtained using purification by flash chromatography (silica gel, Et₂O/hexanes – 1:2).

Colour and state: Colourless oil.

R_f = 0.3 (Et₂O/hexanes – 1:1).

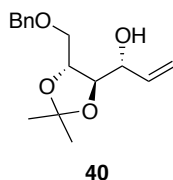
$[\alpha]_D^{20} +3.7$ (*c* 0.5, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.38-7.33 (m, 4H), 7.32-7.27 (m, 1H), 4.60 (s, 2H), 4.51 (app. td, *J* = 4.5, 2.2 Hz, 1H), 4.24 (app. dt, A of ABX₂, *J*_{AB} = 7.9 Hz, *J*_{AX} = 4.9 Hz, 1H), 4.00 (dd, A of ABX, *J*_{AB} = 8.0 Hz, *J*_{BX} = 4.8 Hz, 1H), 3.69 (d, *J* = 5.0 Hz, 2H), 2.83 (d, *J* = 4.7 Hz, 1H), 2.45 (d, *J* = 2.2 Hz, 1H), 1.45 (s, 3H), 1.44 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 137.71 (e), 128.56 (o), 127.95 (o), 127.94 (o), 110.18 (e), 81.09 (e), 80.23 (o), 76.90 (o), 74.96 (e), 73.73 (e), 70.71 (e), 62.64 (o), 27.24 (o), 26.99 (o).

IR (Neat) 3423 (br), 3284 (br), 2988 (w), 2870 (w), 2118 (w), 1497 (w), 1454 (w), 1075 (vs) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4\text{Na}$ 299.1259, found 299.1259.



(*R*)-1-((4*R*,5*R*)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (40**)**⁴³

To a solution of crude alkyne **50** (~71.0 mmol) in THF (280 mL) was added Red-Al[®] (60.9 mL, 3.5 M in toluene, 213 mmol) and the reaction mixture refluxed for *ca.* 13 hours (TLC control). After that time the reaction was cooled to 0 °C and carefully quenched with saturated aqueous Rochelle salt and partitioned between water and EtOAc. Phases were separated and the aqueous layer was washed with EtOAc (2x). The combined organic layers were washed with water (2x), brine, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, Et_2O /hexanes – 1:2.5, 1:2) afforded alkene **40** (12.73 g, 45.8 mmol, 64% yield over 2 steps) as a colourless oil.

$R_f = 0.3$ (Et_2O /hexanes – 1:1).

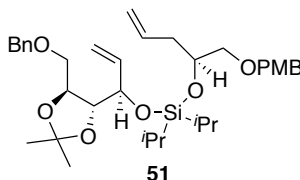
$[\alpha]_D^{20} +15.4$ (*c* 1.0, CHCl_3), Lit. $[\alpha]_D^{20} -21.6$ (*c* 1.1, CHCl_3) for *ent.*^[19]

¹H NMR (500 MHz, CDCl_3) δ 7.36-7.26 (m, 5H), 5.84 (ddd, $J = 17.2, 10.6, 5.6$ Hz, 1H), 5.37 (dt, $J = 17.3, 1.6$ Hz, 1H), 5.20 (dt, $J = 10.6, 1.5$ Hz, 1H), 4.61 (d, A of AB, $J_{AB} = 12.1$ Hz, 1H), 4.57 (d, B of AB, $J_{AB} = 12.1$ Hz, 1H), 4.25 (dddd, $J = 6.8, 5.2, 2.9, 1.4$ Hz, 1H), 4.13 (app. dt, A of ABX₂, $J_{AB} = 8.0$ Hz, $J_{AX} = 5.0$ Hz, 1H), 3.83 (dd, B of ABX, $J_{AB} = 8.0$ Hz, $J_{BX} = 5.5$ Hz, 1H), 3.63 (dd, A of ABX, $J_{AB} = 10.1$ Hz,

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$J_{AX} = 5.1$ Hz, 1H), 3.60 (dd, B of ABX, $J_{AB} = 10.1$ Hz, $J_{BX} = 4.9$ Hz, 1H), 2.81 (d, $J = 2.9$ Hz, 1H), 1.42 (s, 3H), 1.41 (s, 3H).

IR (Neat) 3439 (br), 2986 (w), 2866 (w), 1611 (w), 1080 (s) cm^{-1} .



(4*S*,8*R*)-4-Allyl-8-((4*S*,5*R*)-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-6,6-diisopropyl-1-(4-methoxyphenyl)-2,5,7-trioxa-6-siladec-9-ene (51)

Prepared according the general procedure for the temporary silicon tether formation on 7 mmol scale with 84% yield.

Colour and state: Colourless oil.

FC (SiO_2 , Et_2O /hexanes – 1:10, 1:8, 1:7).

$R_f = 0.56$ (Et_2O /hexanes – 1:2).

$[\alpha]_D^{20} +14.4$ (c 1.0, CHCl_3).

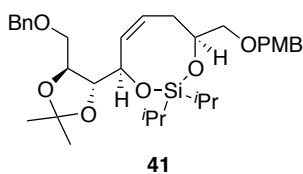
^1H NMR (500 MHz, CDCl_3) δ 7.33-7.31 (m, 4H), 7.29-7.22 (m, 3H), 6.88-6.85 (m, 2H), 5.84 (ddt, $J = 17.3, 10.2, 7.1$ Hz, 1H), 5.80 (ddd, $J = 17.3, 10.4, 6.8$ Hz, 1H), 5.23 (d, $J = 17.3$ Hz, 1H), 5.13 (d, $J = 10.4$ Hz, 1H), 5.06 (dd, $J = 17.6, 1.7$ Hz, 1H), 5.03 (dd, $J = 10.8, 2.0$ Hz, 1H), 4.59 (d, A of AB, $J_{AB} = 12.3$ Hz, 1H), 4.56 (d, B of AB, $J_{AB} = 12.3$ Hz, 1H), 4.46 (dd, $J = 6.4, 5.3$ Hz, 1H), 4.42 (s, 2H), 4.25 (ddd, A of ABXY, $J_{AB} = 7.5$ Hz, $J_{AX} = 6.7$ Hz, $J_{AY} = 2.7$ Hz, 1H), 4.11 (quintet, $J = 5.5$ Hz, 1H), 3.80 (s, 3H), 3.77 (dd, B of ABX, $J_{AB} = 7.7$ Hz, $J_{BX} = 5.0$ Hz, 1H), 3.64 (dd, A of ABX, $J_{AB} = 10.3$ Hz, $J_{AX} = 2.8$ Hz, 1H), 3.51 (dd, B of ABX, $J_{AB} = 10.3$ Hz, $J_{BX} = 6.5$ Hz, 1H), 3.41 (dd, A of ABX, $J_{AB} = 9.5$ Hz, $J_{AX} = 5.3$ Hz, 1H), 3.36 (dd, B of ABX, $J_{AB} = 9.5$ Hz, $J_{BX} = 5.8$ Hz, 1H), 2.40 (app. dt, A of ABX_2 , $J_{AB} = 13.6$ Hz, $J_{AX} = 6.7$

Hz, 1H), 2.30 (app. dtd, B of ABX₂Y, $J_{AB} = 13.6$ Hz, $J_{BX} = 6.7$ Hz, $J_{BY} = 1.0$ Hz, 1H), 1.41 (s, 6H), 1.04-0.92 (m, 2H), 1.02 (s, 3H), 1.00 (s, 6H), 0.99 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 159.10 (e), 138.17 (e), 137.80 (o), 134.49 (o), 130.53 (e), 129.24 (o), 128.31 (o), 127.73 (o), 127.56 (o), 117.25 (e), 116.86 (e), 113.68 (o), 109.41 (e), 80.59 (o), 77.33 (o), 74.15 (o), 73.43 (e), 73.26 (e), 72.89 (e), 71.63 (e), 70.78 (o), 55.28 (o), 39.15 (e), 27.17 (o), 17.50 (o), 17.45 (o), 17.43 (o), 12.85 (o), 12.81 (o).

IR (Neat) 2940 (w), 2866 (m), 1641 (w), 1613 (w), 1587 (w), 1084 (vs), 1036 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₃₅H₅₂O₇NaSi 635.3380, found 635.3379.



(4*S*,8*R*,*Z*)-8-((4*S*,5*R*)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diisopropyl-4-(((4-methoxybenzyl)oxy)methyl)-5,8-dihydro-4*H*-1,3,2-dioxasilocine (41)

Prepared according the general procedure for the temporary silicon-tethered ring-closing metathesis on 5 mmol scale with 99% yield.

Colour and state: Colourless oil.

FC (SiO₂, Et₂O/hexanes – 1:5).

R_f = 0.58 (Et₂O/hexanes – 1:1).

$[\alpha]_{\text{D}}^{20} +13.3$ (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, C₆D₆) δ 7.32-7.31 (m, 2H), 7.20-7.15 (m, 4H), 7.10-7.07 (m, 1H), 6.80-6.77 (m, 2H), 6.03 (dd, $J = 11.2, 6.1$ Hz, 1H), 5.63 (q, $J = 9.5$ Hz, 1H),

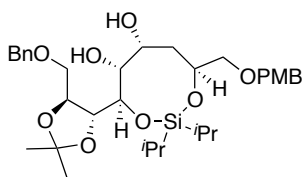
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4.62 (t, $J = 6.5$ Hz, 1H), 4.47 (s, 2H), 4.43 (ddd, $J = 7.7, 5.3, 2.6$ Hz, 1H), 4.34 (d, A of AB, $J_{AB} = 11.7$ Hz, 1H), 4.30 (d, B of AB, $J_{AB} = 11.7$ Hz, 1H), 4.24 (app. dtd, $J = 7.4, 5.7, 3.7$ Hz, 1H), 4.08 (t, $J = 7.2$ Hz, 1H), 3.81 (dd, A of ABX, $J_{AB} = 10.4$ Hz, $J_{AX} = 2.8$ Hz, 1H), 3.63 (dd, B of ABX, $J_{AB} = 10.4$ Hz, $J_{BX} = 5.5$ Hz, 1H), 3.47 (dd, A of ABX, $J_{AB} = 9.1$ Hz, $J_{AX} = 5.3$ Hz, 1H), 3.32-3.29 (m, 1H), 3.30 (s, 3H), 2.59 (ddd, A of ABXY, $J_{AB} = 13.9$ Hz, $J_{AX} = 7.5$ Hz, $J_{AY} = 6.5$ Hz, 1H), 2.37 (ddd, B of ABXY, $J_{AB} = 13.5$ Hz, $J_{BX} = 9.5$ Hz, $J_{BY} = 3.7$ Hz, 1H), 1.45 (s, 3H), 1.44 (s, 3H), 1.12 (d, $J = 7.5$ Hz, 3H), 1.11 (d, $J = 7.4$ Hz, 3H), 1.10 (s, 3H), 1.09 (s, 3H), 1.08-1.01 (m, 1H), 0.94 (septet, $J = 7.4$ Hz, 1H).

^{13}C NMR (125 MHz, C_6D_6) δ 159.81 (e), 139.09 (e), 134.50 (o), 130.94 (e), 129.48 (o), 129.40 (o), 128.55 (o), 127.84 (o), 127.68 (o), 114.12 (o), 109.62 (e), 80.90 (o), 80.25 (o), 73.60 (e), 73.50 (e), 73.26 (o), 73.11 (e), 72.04 (e), 71.83 (o), 54.79 (o), 32.93 (e), 27.59 (o), 27.50 (o), 17.94 (o), 17.86 (o), 17.79 (o), 13.62 (o), 13.32 (o).

IR (Neat) 2939 (m), 2865 (m), 1612 (w), 1586 (w), 1513 (m), 1246 (s), 1086 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{33}\text{H}_{48}\text{O}_7\text{NaSi}$ 607.3067 found 607.3063.



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(4*R*,5*R*,6*R*,8*S*)-4-((4*R*,5*S*)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diisopropyl-8-(((4-methoxybenzyl)oxy)methyl)-1,3,2-dioxasilocane-5,6-diol (52)

Prepared according the general procedure for the dihydroxylation of cyclic silaketals on 1.08 mmol scale with 96% yield.

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Colour and state: Colourless oil.

FC (SiO₂, Et₂O/hexanes – 1:1, 2:1, 3:1, 20:1).

R_f = 0.07 (Et₂O/hexanes – 1:1).

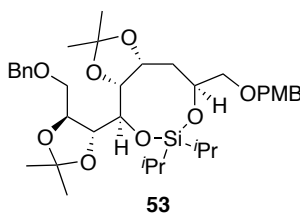
$[\alpha]_{\text{D}}^{20} +7.2$ (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.34-7.33 (m, 4H), 7.31-7.27 (m, 1H), 7.26-7.24 (m, 2H), 6.88-6.86 (m, 2H), 4.64 (d, A of AB, J_{AB} = 12.1 Hz, 1H), 4.52 (d, B of AB, J_{AB} = 12.1 Hz, 1H), 4.49 (d, A of AB, J_{AB} = 12.0 Hz, 1H), 4.47 (d, B of AB, J_{AB} = 11.9 Hz, 1H), 4.31 (app. dq, J = 9.9, 5.1 Hz, 1H), 4.30 (app. td, J = 7.2, 3.1 Hz, 1H), 4.18 (app. tt, J = 8.6, 2.9 Hz, 1H), 4.04 (dd, a of ABX, J_{AB} = 8.4 Hz, J_{AX} = 6.5 Hz, 1H), 3.97 (app. dt, B of ABX₂, J_{AB} = 8.5 Hz, J_{BX} = 2.4 Hz, 1H), 3.84 (B of ABX, J_{AB} = 7.4 Hz, J_{BX} = 6.8 Hz, 1H), 3.80 (s, 3H), 3.69 (dd, A of ABX, J_{AB} = 10.3 Hz, J_{AX} = 3.0 Hz, 1H), 3.56 (dd, B of ABX, J_{AB} = 10.3 Hz, J_{BX} = 6.8 Hz, 1H), 3.47 (dd, A of ABX, J_{AB} = 9.7 Hz, J_{AX} = 5.7 Hz, 1H), 3.38 (dd, B of ABX, J_{AB} = 9.7 Hz, J_{BX} = 5.1 Hz, 1H), 3.22 (d, J = 2.7 Hz, 1H), 2.39 (d, J = 8.5 Hz, 1H), 2.11 (ddd, A of ABXY, J_{AB} = 14.0 Hz, J_{AX} = 9.9 Hz, J_{AY} = 4.0 Hz, 1H), 1.76 (ddd, B of ABXY, J_{AB} = 14.0 Hz, J_{BX} = 10.2 Hz, J_{BY} = 3.8 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.08 (d, J = 5.4 Hz, 3H), 1.05-1.00 (m, 4H), 0.97 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.85 (septet, J = 5.8 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 159.24 (e), 137.86 (e), 130.40 (e), 129.31 (o), 128.46 (o), 128.01 (o), 127.85 (o), 113.82 (o), 109.99 (e), 81.35 (o), 78.72 (o), 77.16 (o), 74.97 (e), 74.93 (o), 73.72 (e), 73.11 (e), 71.80 (e), 68.55 (o), 67.72 (o), 55.33 (o), 35.88 (e), 27.20 (o), 27.14 (o), 17.80 (o), 17.55 (o), 17.21 (o), 12.45 (o), 11.76 (o).

IR (Neat) 3448 (br), 2932 (m), 2866 (m), 1612 (w), 1587 (w), 1513 (m), 1247 (s), 1087 (s) 1035 (s) cm⁻¹.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{33}H_{50}O_9NaSi$ 641.3122 found 641.3098.



(3a*R*,4*R*,8*S*,9a*R*)-4-((4*R*,5*S*)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-6,6-diisopropyl-8-(((4-methoxybenzyl)oxy)methyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3,2]dioxasilocine (53)

Prepared according the general procedure for the $VO(OTf)_2$ catalysed acetonide formation on 0.986 mmol scale with 99% yield.

Colour and state: Colourless oil.

FC (SiO_2 , Et_2O /hexanes – 1:7, 1:5).

R_f = 0.58 (Et_2O /hexanes – 1:1).

$[\alpha]_D^{20}$ –3.3 (c 1.0, $CHCl_3$).

1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (m, 4H), 7.27-7.26 (m, 3H), 6.88-6.77 (m, 2H), 4.97 (d, A of AB, J_{AB} = 9.4 Hz, 1H), 4.56 (d, B of AB, J_{AB} = 9.4 Hz, 1H), 4.53 (d, A of AB, J_{AB} = 13.8 Hz, 1H), 4.49 (d, B of AB, J_{AB} = 12.0 Hz, 1H), 4.48 (ddd, J = 7.5, 6.6, 2.7 Hz, 1H), 4.40 (ddd, A of ABXY, J_{AB} = 10.3 Hz, J_{AX} = 5.4 Hz, J_{AY} = 1.5 Hz, 1H), 4.31 (dd, A of ABX, J_{AB} = 9.7 Hz, J_{AX} = 2.0 Hz, 1H), 4.25 (app. dq, J = 6.2, 3.1 Hz, 1H), 4.14 (dd, B of ABX, J_{AB} = 8.1 Hz, J_{BX} = 2.0 Hz, 1H), 3.85 (dd, B of ABX, J_{AB} = 9.7 Hz, J_{BX} = 5.4 Hz, 1H), 3.80 (s, 3H), 3.68 (dd, A of ABX, J_{AB} = 10.6 Hz, J_{AX} = 2.6 Hz, 1H), 3.55 (dd, B of ABX, J_{AB} = 10.6 Hz, J_{BX} = 6.9 Hz, 1H), 3.51 (dd, A of ABX, J_{AB} = 9.7 Hz, J_{AX} = 5.8 Hz, 1H), 3.43 (dd, B of ABX, J_{AB} = 9.6 Hz, J_{BX} = 7.0 Hz, 1H), 2.24 (ddd, A of ABXY, J_{AB} = 15.6 Hz, J_{AX} = 10.0 Hz, J_{AY} = 5.9 Hz, 1H), 1.96 (app. dt, B of ABX₂, J_{AB} = 15.4 Hz, J_{BX} = 2.3 Hz, 1H), 1.43 (s, 3H),

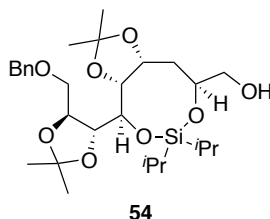
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1.42 (s, 3H), 1.35 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.08 (d, $J = 5.8$ Hz, 3H), 1.04-0.99 (m, 1H), 1.01 (d, $J = 7.4$ Hz, 3H), 1.00 (d, $J = 7.4$ Hz, 3H), 0.91 (septet, $J = 7.2$ Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3) δ 159.27 (e), 138.35 (e), 130.53 (e), 129.26 (o), 128.44 (o), 127.75 (o), 127.67 (o), 113.88 (o), 109.17 (e), 107.75 (e), 79.23 (o), 78.03 (o), 74.85 (o), 73.77 (o), 73.42 (e), 73.12 (e), 73.07 (e), 71.77 (e), 69.25 (o), 68.27 (o), 55.37 (o), 33.52 (e), 27.99 (o), 27.38 (o), 27.19 (o), 25.60 (o), 17.58 (o), 17.55 (o), 17.41 (o), 17.35 (o), 12.18 (o), 12.09 (o).

IR (Neat) 2936 (w), 2866 (w), 1613 (w), 1587 (w), 1513 (m), 1245 (s), 1087 (s) 1038 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{36}\text{H}_{54}\text{O}_9\text{NaSi}$ 681.3435 found 681.3418.



((3a*R*,4*R*,8*S*,9a*R*)-4-((4*R*,5*S*)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-6,6-diisopropyl-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3,2]dioxasilocin-8-yl)methanol (54)

Prepared according the general procedure for the chemoselective PMB ether deprotection on 0.968 mmol scale with 96% yield.

Colour and state: Colourless oil.

$[\alpha]_{\text{D}}^{20} +4.7$ (c 0.5, CHCl_3).

FC (SiO_2 , Et_2O /hexanes – 1:3, 1:2).

$R_f = 0.28$ (Et_2O /hexanes – 1:1).

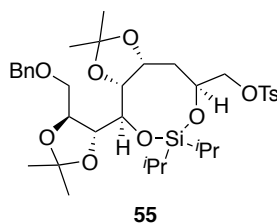
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¹H NMR (500 MHz, CDCl₃) δ 7.35-7.30 (m, 4H), 7.29-7.24 (m, 1H), 4.66 (d, A of AB, J_{AB} = 12.4 Hz, 1H), 4.55 (d, B of AB, J_{AB} = 12.4 Hz, 1H), 4.48 (ddd, A of ABXY, J_{AB} = 8.0 Hz, J_{AX} = 7.0 Hz, J_{AY} = 2.8 Hz, 1H), 4.40 (ddd, J = 10.2, 5.4, 1.4 Hz, 1H), 4.30 (dd, A of ABX, J_{AB} = 9.8 Hz, J_{AX} = 2.0 Hz, 1H), 4.16 (ddd, J = 6.9, 4.0, 2.9 Hz, 1H), 4.14 (dd, B of ABX, J_{AB} = 8.1 Hz, J_{BX} = 2.0 Hz, 1H), 3.85 (dd, B of ABX, J_{AB} = 9.8 Hz, J_{BX} = 5.4 Hz, 1H), 3.65 (dd, A of ABX, J_{AB} = 10.6 Hz, J_{BX} = 2.8 Hz, 1H), 3.61 (dd, A of ABXY, J_{AB} = 11.1 Hz, J_{AX} = 7.8 Hz, J_{AY} = 3.4 Hz, 1H), 3.55 (dd, B of ABX, J_{AB} = 10.6 Hz, J_{BX} = 6.9 Hz, 1H), 3.52 (dd, B of ABXY, J_{AB} = 10.9 Hz, J_{BX} = 9.0 Hz, J_{BY} = 4.4 Hz, 1H), 2.29 (ddd, A of ABXY, J_{AB} = 15.6 Hz, J_{AX} = 10.1 Hz, J_{AY} = 6.6 Hz, 1H), 2.15 (dd, J = 9.0, 3.6 Hz, 1H), 1.72 (ddd, A of ABXY, J_{AB} = 15.6 Hz, J_{BX} = 2.6 Hz, J_{BY} = 1.9 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.16-1.05 (m, 1H), 1.11 (s, 6H), 1.08 (d, J = 6.3 Hz, 3H), 1.02 (d, J = 6.7 Hz, 3H), 1.01 (d, J = 6.2 Hz, 3H), 0.98-0.91 (m, 1H).

¹³C NMR (125 MHz, CDCl₃) 138.22 (e), 128.43 (o), 127.72 (o), 127.69 (o), 109.18 (e), 107.98 (e), 79.37 (o), 77.75 (o), 74.66 (o), 73.85 (o), 73.39 (e), 71.71 (e), 69.43 (o), 69.04 (o), 66.36 (e), 33.40 (e), 27.95 (o), 27.30 (o), 27.14 (o), 25.50 (o), 17.55 (o), 17.52 (o), 17.41 (o), 17.33 (o), 11.97 (o), 11.91 (o).

IR (Neat) 3474 (br), 2985 (w), 2934 (w), 2867 (w), 1497 (w), 1455 (w), 1040 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₂₈H₄₆O₈NaSi 561.2860 found 561.2849.



((3a*S*,4*S*,8*R*,9a*S*)-4-((4*R*,5*S*)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-6,6-diisopropyl-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3,2]dioxasilocin-8-yl)methyl 4-methylbenzenesulfonate (55)

Prepared according the general procedure for tosylation on 0.223 mmol scale with 96% yield.

Colour and state: Colourless oil.

$R_f = 0.51$ (Et₂O/hexanes – 1:1).

$[\alpha]_D^{20} +2.2$ (*c* 0.5, CHCl₃).

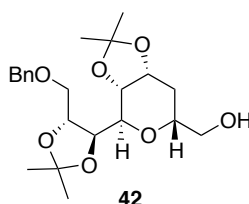
¹H NMR (500 MHz, CDCl₃) δ 7.80-7.36 (m, 2H), 7.36-7.28 (m, 6H), 6.27-6.24 (m, 1H), 4.65 (d, A of AB, $J_{AB} = 12.4$ Hz, 1H), 4.53 (d, B of AB, $J_{AB} = 12.4$ Hz, 1H), 4.44 (ddd, A of ABXY, $J_{AB} = 8.0$ Hz, $J_{AX} = 6.9$ Hz, $J_{AY} = 2.8$ Hz, 1H), 4.49-4.24 (m, 2H), 4.24 (d, A of ABX, $J_{AB} = 10.0$ Hz, $J_{AX} = 2.2$ Hz, 1H), 4.11 (dd, B of ABX, $J_{AB} = 8.1$ Hz, $J_{BX} = 2.1$ Hz, 1H), 4.00 (dd, A of ABX, $J_{AB} = 9.9$ Hz, $J_{AX} = 6.7$ Hz, 1H), 3.92 (dd, B of ABX, $J_{AB} = 9.9$ Hz, $J_{BX} = 5.3$ Hz, 1H), 3.63 (A of ABX, $J_{AB} = 10.5$ Hz, $J_{AX} = 2.9$ Hz, 1H), 3.53 (B of ABX, $J_{AB} = 10.6$ Hz, $J_{BX} = 6.8$ Hz, 1H), 2.44 (s, 3H), 2.23 (ddd, A of ABXY, $J_{AB} = 15.6$ Hz, $J_{AX} = 10.3$ Hz, $J_{AY} = 6.5$ Hz, 1H), 1.74 (ddd, B of ABXY, $J_{AB} = 15.6$ Hz, $J_{BX} = 3.3$ Hz, $J_{BY} = 1.9$ Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 1.31 (s, 3H), 1.09 (s, 3H), 1.07 (d, $J = 2.2$ Hz, 1H), 1.05-0.98 (m, 1H), 0.96 (d, $J = 7.0$ Hz, 1H), 0.93 (d, $J = 6.9$ Hz, 1H), 0.87 (d of quintets, B of ABX₅, $J_{AB} = 7.0$ Hz, $J_{BX} = 6.7$ Hz, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 144.90 (e), 138.13 (e), 132.86 (e), 129.91 (o), 128.36 (o), 127.94 (o), 127.64 (o), 109.12 (e), 107.98 (e), 79.09 (o), 77.62 (o), 74.59

(o), 73.32 (e), 73.28 (o), 72.10 (e), 71.61 (e), 69.02 (o), 66.56 (o), 33.04 (e), 27.87 (o), 27.22 (o), 27.05 (o), 25.42 (o), 21.68 (o), 17.32 (o), 17.27 (o), 17.17 (o), 17.07 (o), 11.87 (o), 11.78 (o).

IR (Neat) 2985 (w), 2937 (w), 2868 (w), 1599 (w), 1497 (w), 1455 (w), 1367 (s), 1176 (s) cm^{-1} .

HRMS (ESI, $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{35}\text{H}_{52}\text{O}_{10}\text{NaSiS}$ 715.2948 found 715.2932.



((3a*S*,4*S*,6*S*,7a*S*)-4-((4*R*,5*S*)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl)methanol (42)

To a solution of tosylate **55** (0.0343 g, 0.049 mmol) in THF (1 mL) was added TBAF (0.124 mL, 1 M in THF, 0.124 mmol). After *ca.* 30 min (TLC control) the reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and treated with $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.020 mL, 0.074 mmol). The reaction was warmed to room temperature and stirred for *ca.* 2 h (TLC control), before it was quenched with saturated aqueous NH_4Cl and partitioned between water and EtOAc. Phases were separated and the aqueous layer was washed with EtOAc (2x). The combined organic layers were washed with water, brine, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, EtOAc/hexanes – 1:2.5, 1:1.5) afforded alcohol **42** (0.0157 g, 0.038 mmol, 78% yield) as a colourless oil.

$R_f = 0.3$ (EtOAc/hexanes – 1:1).

$[\alpha]_D^{20} +1.5$ (*c* 0.5, CHCl_3).

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¹H NMR (500 MHz, CDCl₃) δ 7.38-7.33 (m, 4H), 7.32-7.22 (m, 1H), 4.59 (s, 2H), 4.34 (app. dt, A of ABX₂, J_{AB} = 8.5 Hz, J_{AX} = 6.1 Hz, 1H), 4.26 (app. dt, J = 8.7, 4.7 Hz, 1H), 4.24 (app. dt, J = 7.4, 6.0 Hz, 1H), 4.10 (dd, B of ABX, J_{AB} = 8.3 Hz, J_{BX} = 3.5 Hz, 1H), 3.93 (dd, J = 5.3, 3.6 Hz, 1H), 3.83 (app. ddt, J = 10.2, 7.3, 3.6 Hz, 1H), 3.65-3.61 (m, 3H), 3.52 (dd, B of ABX, J_{AB} = 11.8 Hz, J_{AX} = 3.2 Hz, 1H), 2.01 (br s, 1H), 1.93 (ddd, A of ABXY, J_{AB} = 13.8 Hz, J_{AX} = 5.9 Hz, J_{AY} = 4.5 Hz, 1H), 1.63 (app. dt, B of ABX₂, J_{AB} = 13.7 Hz, J_{BX} = 9.2 Hz, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 137.97 (e), 128.55 (o), 127.91 (o), 110.03 (e), 108.77 (e), 79.33 (o), 76.89 (o), 73.63 (e), 72.47 (o), 71.43 (o), 71.28 (o), 71.17 (o), 70.57 (e), 64.81 (e), 29.09 (e), 28.07 (o), 27.29 (o), 27.02 (o), 25.94 (o).

IR (Neat) 3470 (br), 2985 (w), 2936 (w), 2873 (w), 1635 (w), 1062 (s) cm⁻¹.

HRMS (ESI, [M+Na]⁺) calcd for C₂₂H₃₂O₇Na 431.2046 found 431.2042.

6.10 References

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6.11 Appendix C. ^1H and APT Spectrums for Compound 42